



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

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Stuart J. Pocock, PhD, Christie M. Ballantyne, MD, on Behalf of the

**REDUCE-IT** Investigators



# 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.

# REDUCE-IT Study PI and Committees



## **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

## **Steering Committee**

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

## **Data Monitoring Committee**

Brian Olshansky MD (Chair), Mina Chung MD, Al Hallstrom PhD, Lesly A. Pearce MS (independent statistician)  
Independent Statistical Center Support for Data Monitoring Committee: Cyrus Mehta PhD, Rajat Mukherjee PhD

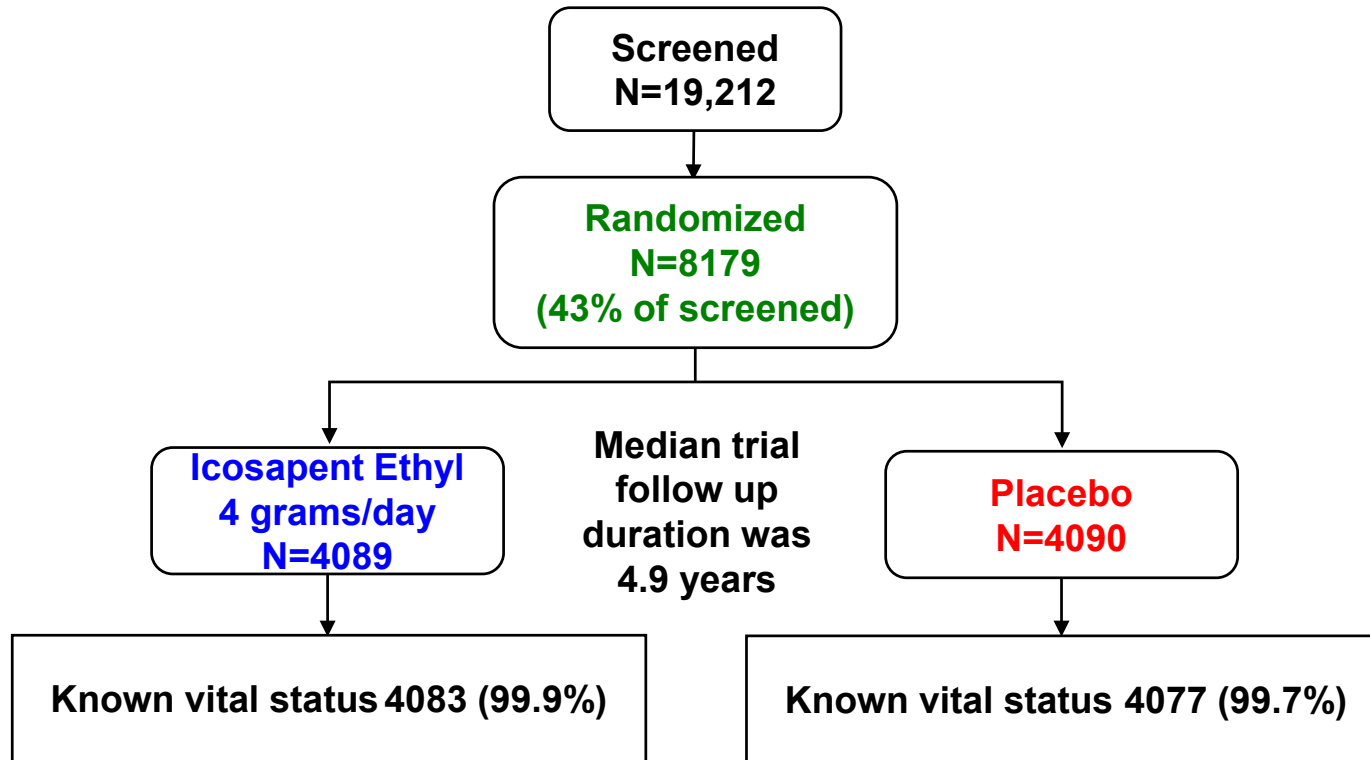
## **Clinical Endpoint Committee**

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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

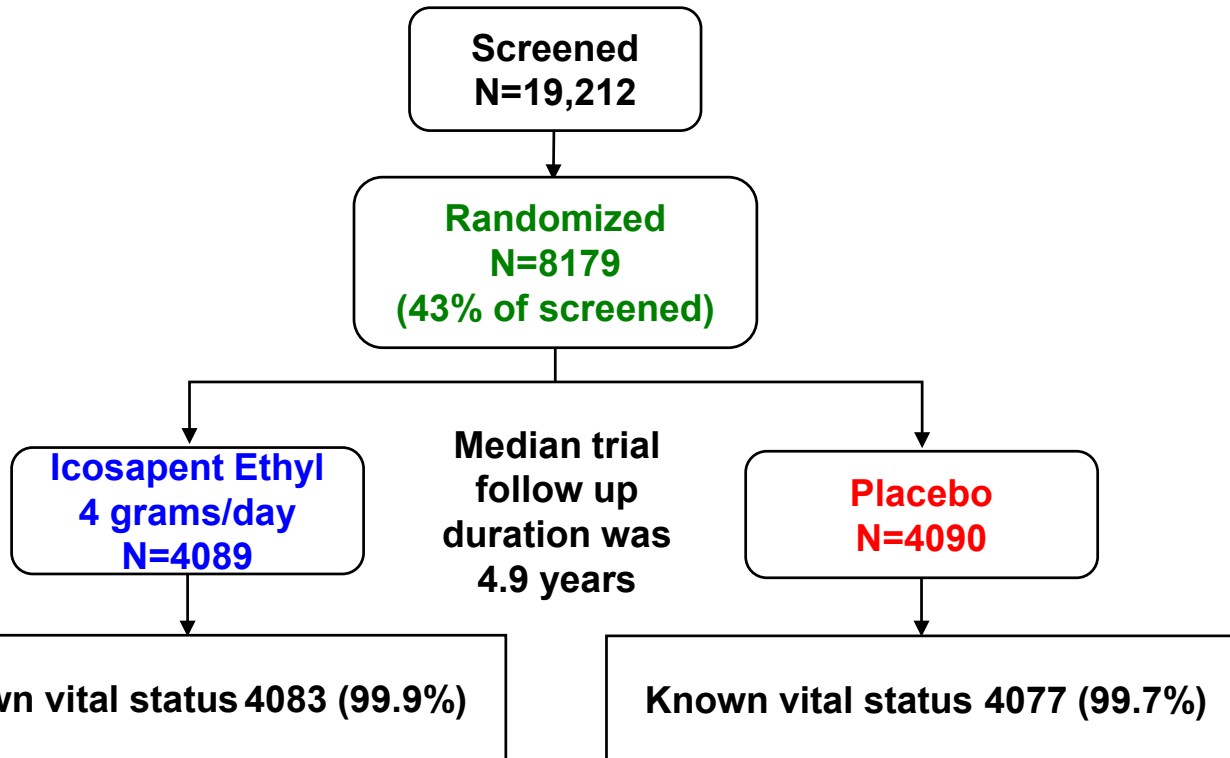
**Key Secondary Endpoint Events:** CV death, nonfatal MI, nonfatal stroke

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

# REDUCE-IT Design



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



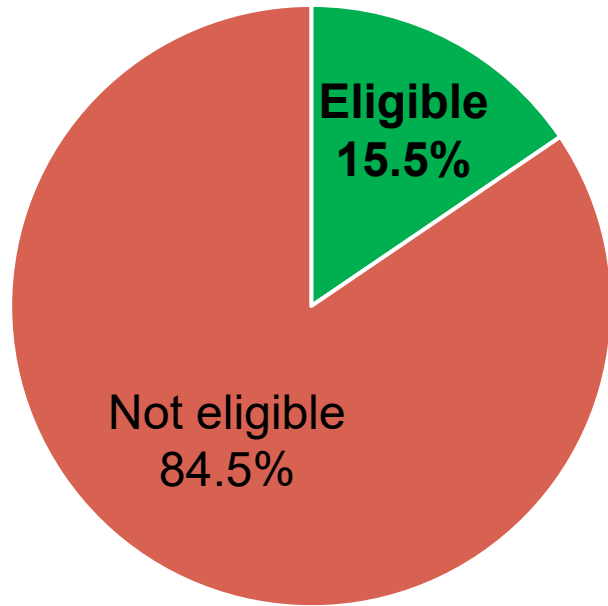
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**Key Secondary Endpoint Events:** CV death, nonfatal MI, nonfatal stroke

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# Generalizability of **REDUCE-IT** in Patients with Stable CAD

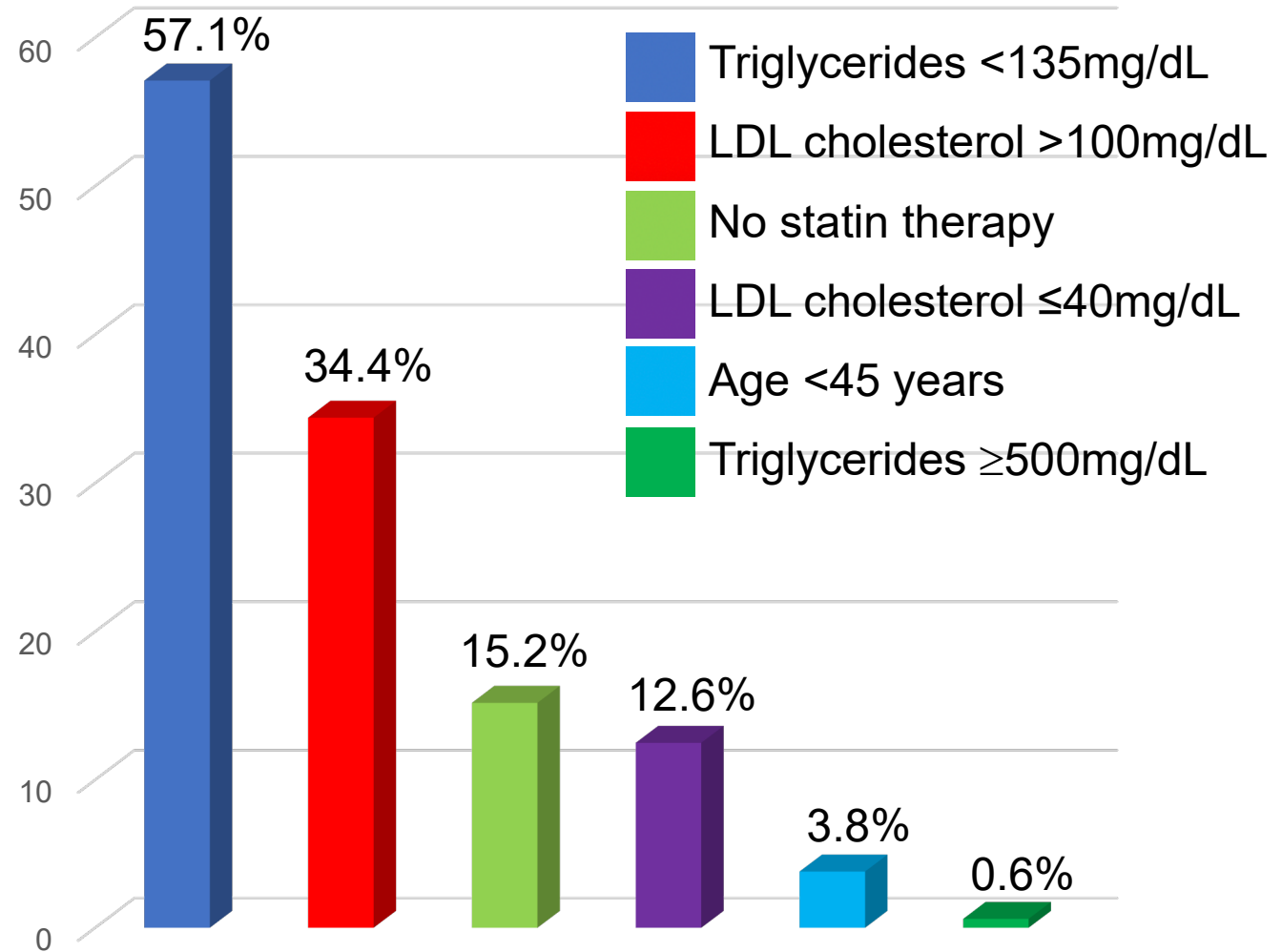
*An analysis of 24,146 patients from the CLARIFY registry*



## Key Inclusion Criteria for CLARIFY Analysis

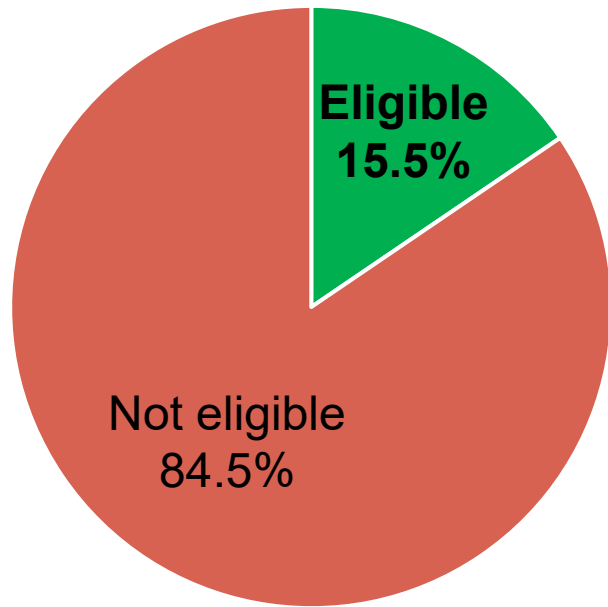
- Statin-treated men or women
- Age  $\geq 45$  years with either established CV disease OR age  $\geq 50$  years with diabetes mellitus and at least one additional CV risk factor
- AND triglycerides  $\geq 135$  and  $< 500$  mg/dL
- AND LDL-cholesterol  $> 40$  and  $\leq 100$  mg/dL

## Main reasons for exclusion



# Generalizability of **REDUCE-IT** in Patients with Stable CAD

*An analysis of 24,146 patients from the CLARIFY registry*

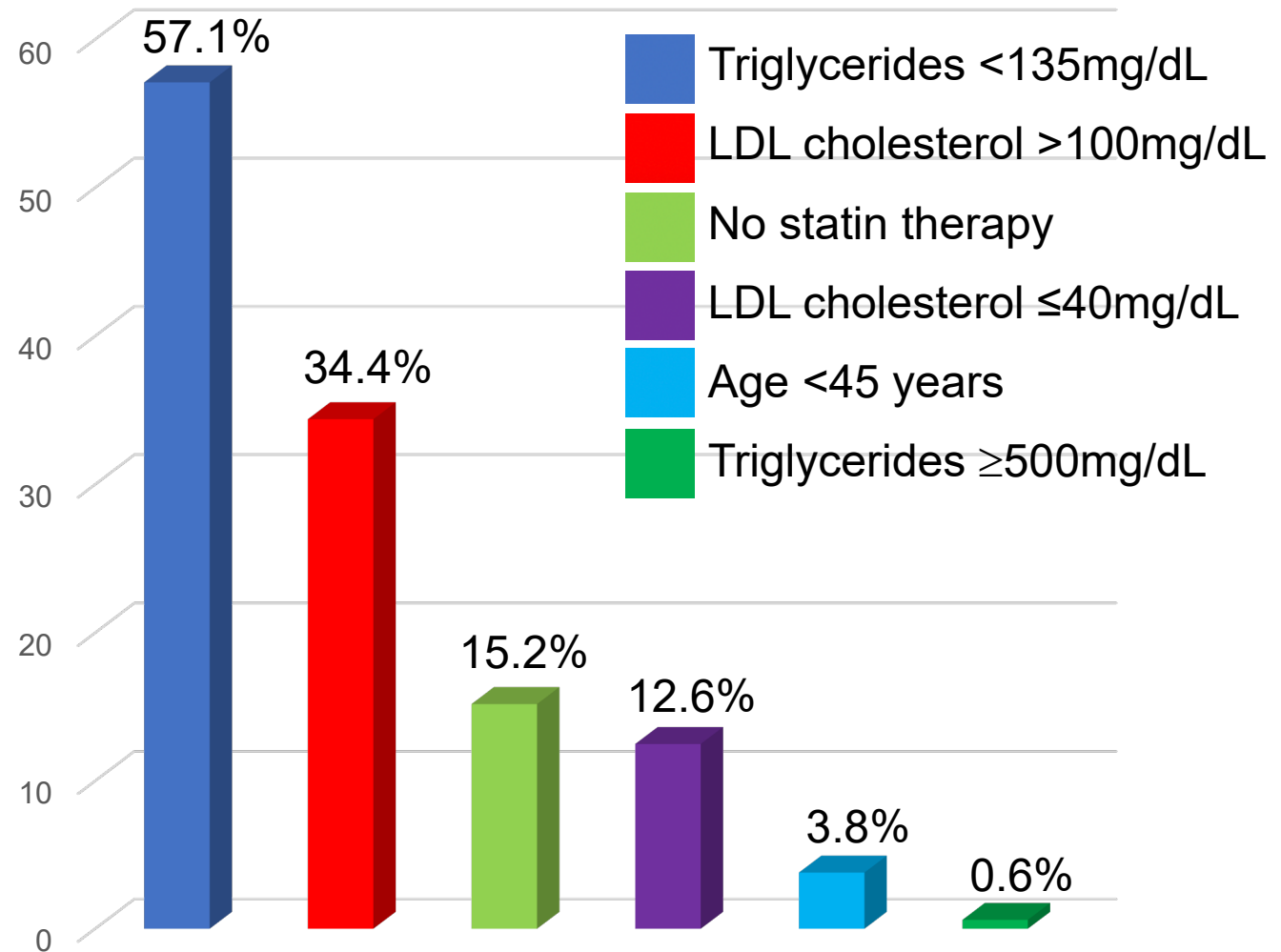


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- AND triglycerides  $\geq 135$  and  $< 500$  mg/dL
- AND LDL-cholesterol  $> 40$  and  $\leq 100$  mg/dL

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

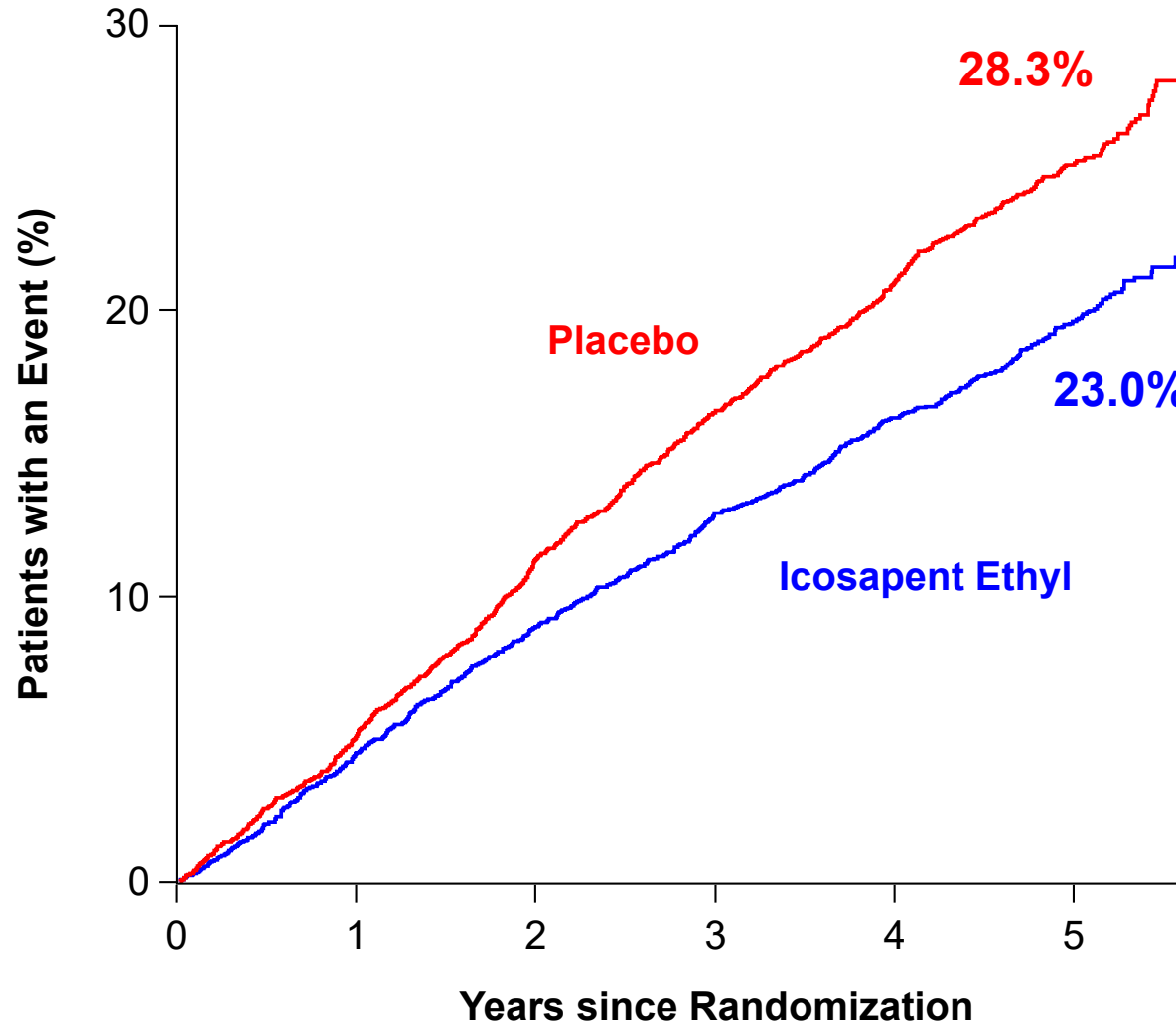
## Main reasons for exclusion



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%**

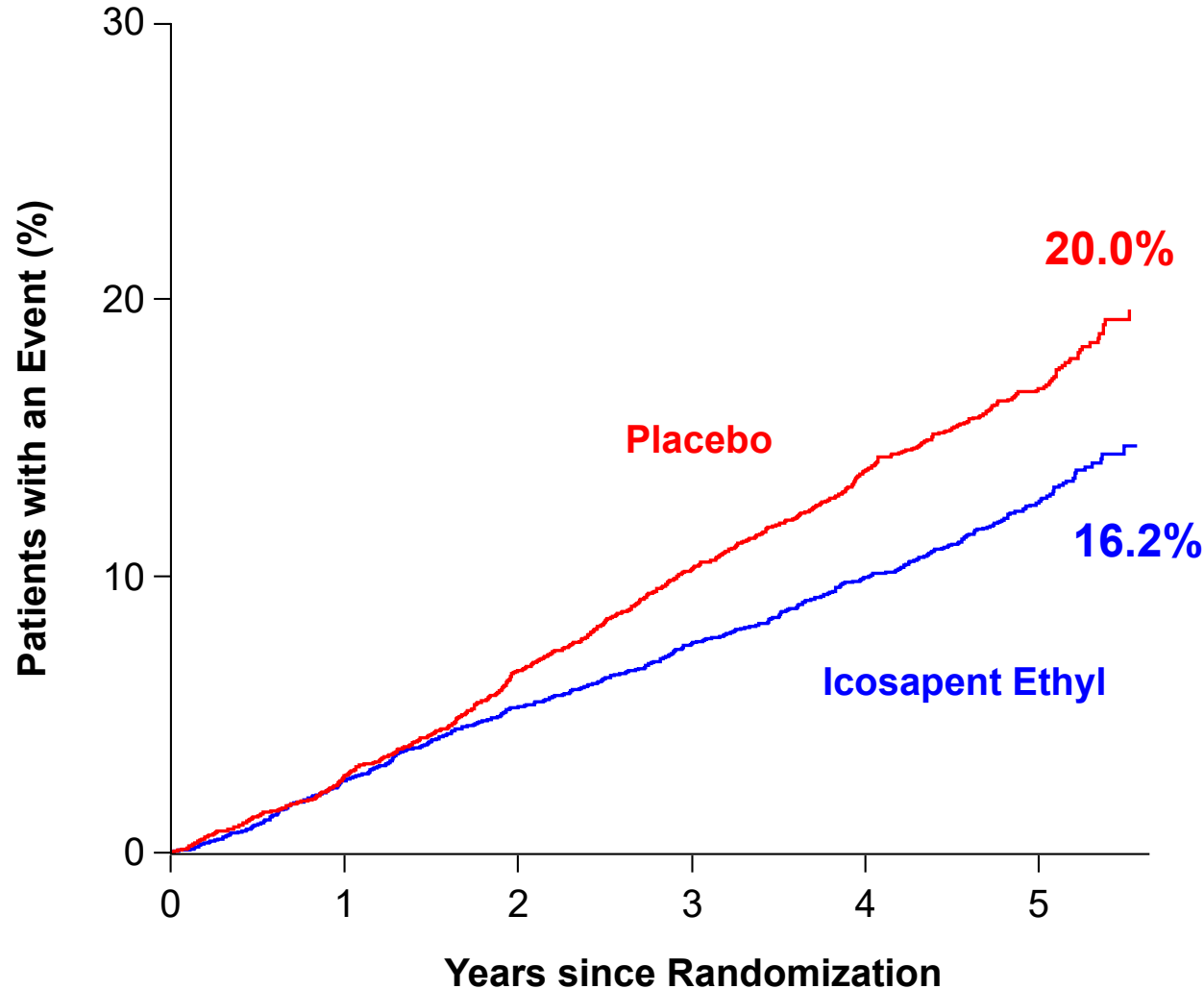
**ARR = 4.8%**

**NNT = 21** (95% CI, 15–33)

**P=0.00000001**



# Key Secondary End Point: CV Death, MI, Stroke



**Hazard Ratio, 0.74**

(95% CI, 0.65–0.83)

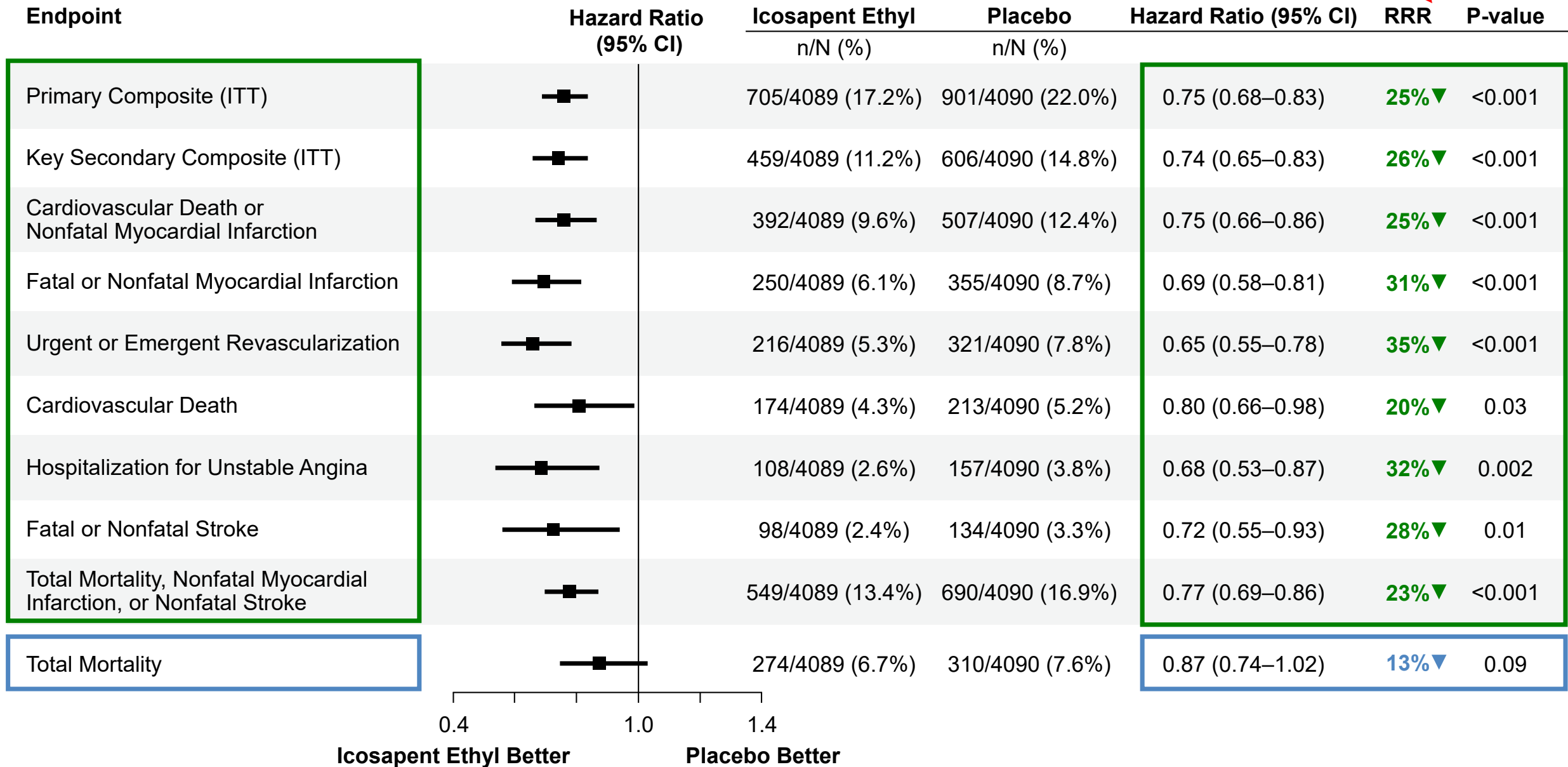
**RRR = 26.5%**

**ARR = 3.6%**

**NNT = 28** (95% CI, 20–47)

**P=0.0000006**

# Prespecified Hierarchical Testing



# 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	

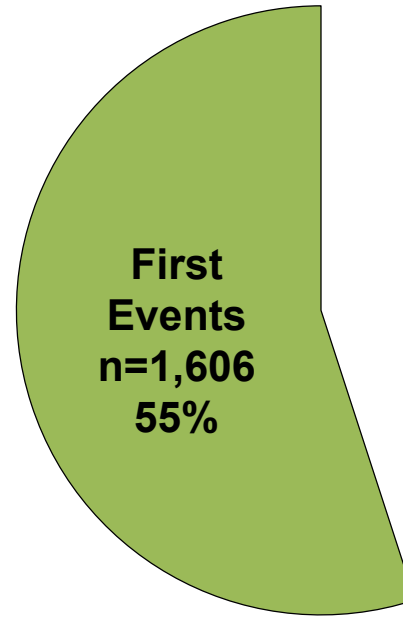
\*Baseline TG calculated as average of final screening TG and subsequent TG value from date of randomization.

# Key Medical Therapy



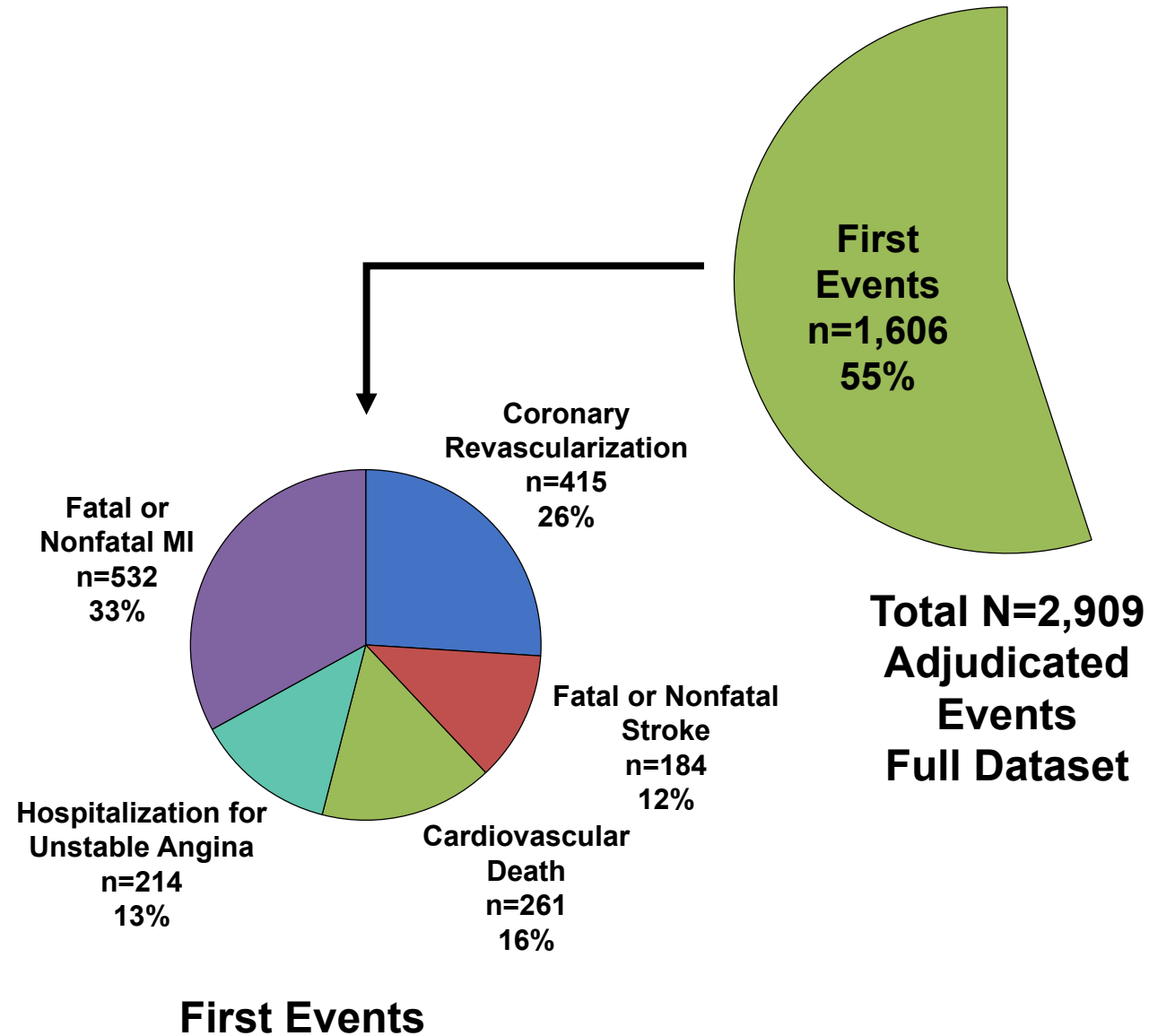
	<b>Icosapent Ethyl (N=4089)</b>	<b>Placebo (N=4090)</b>
Antiplatelet	3257 (79.7%)	3236 (79.1%)
One Antiplatelet	2416 (59.1%)	2408 (58.9%)
Two or More Antiplatelets	841 (20.6%)	828 (20.2%)
Anticoagulant	385 (9.4%)	390 (9.5%)
ACEi or ARB	3164 (77.4%)	3176 (77.7%)
Beta Blocker	2902 (71.0%)	2880 (70.4%)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

# Proportions of First and Subsequent Events

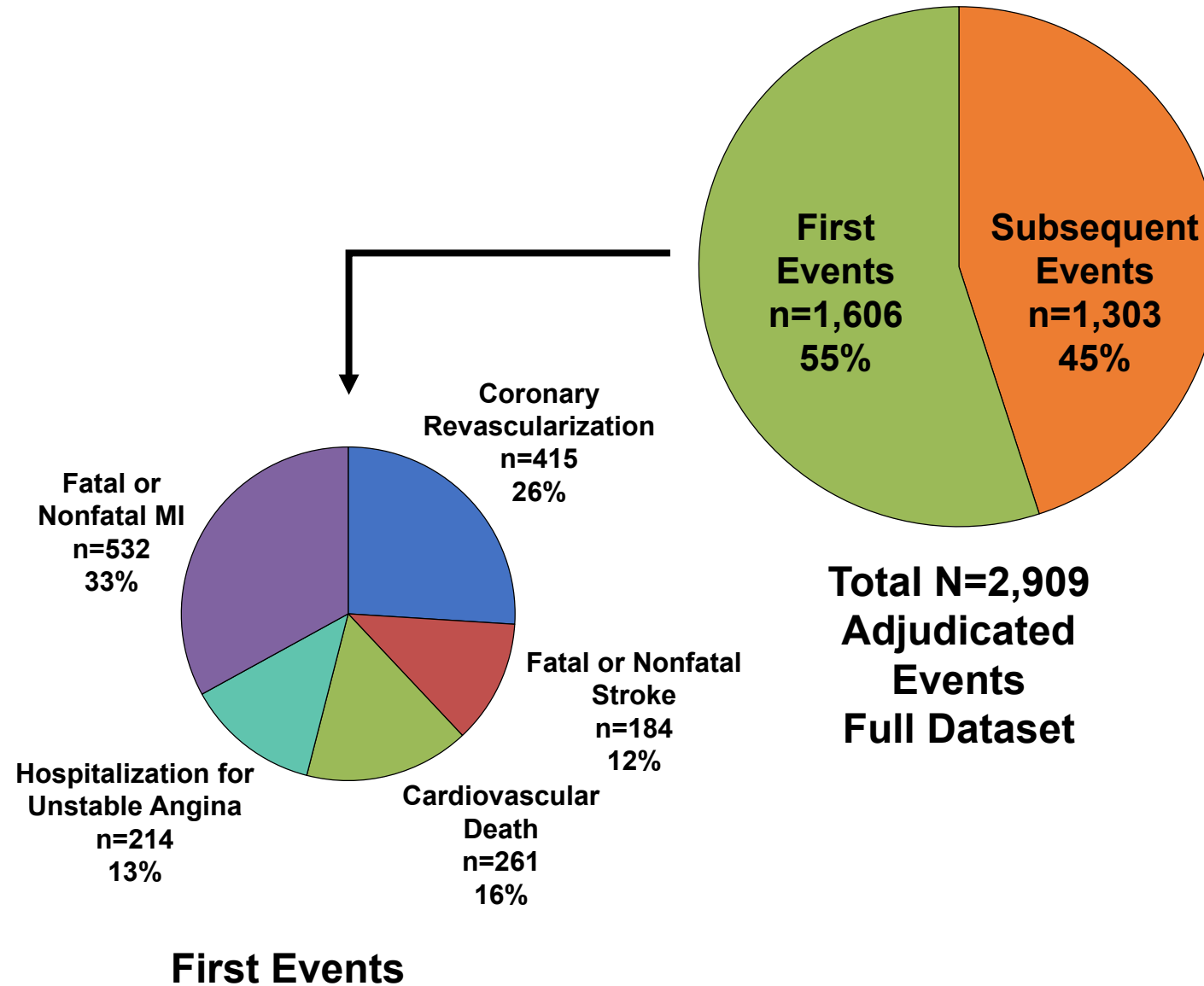


**Total N=2,909**  
**Adjudicated**  
**Events**  
**Full Dataset**

# Proportions of First and Subsequent Events

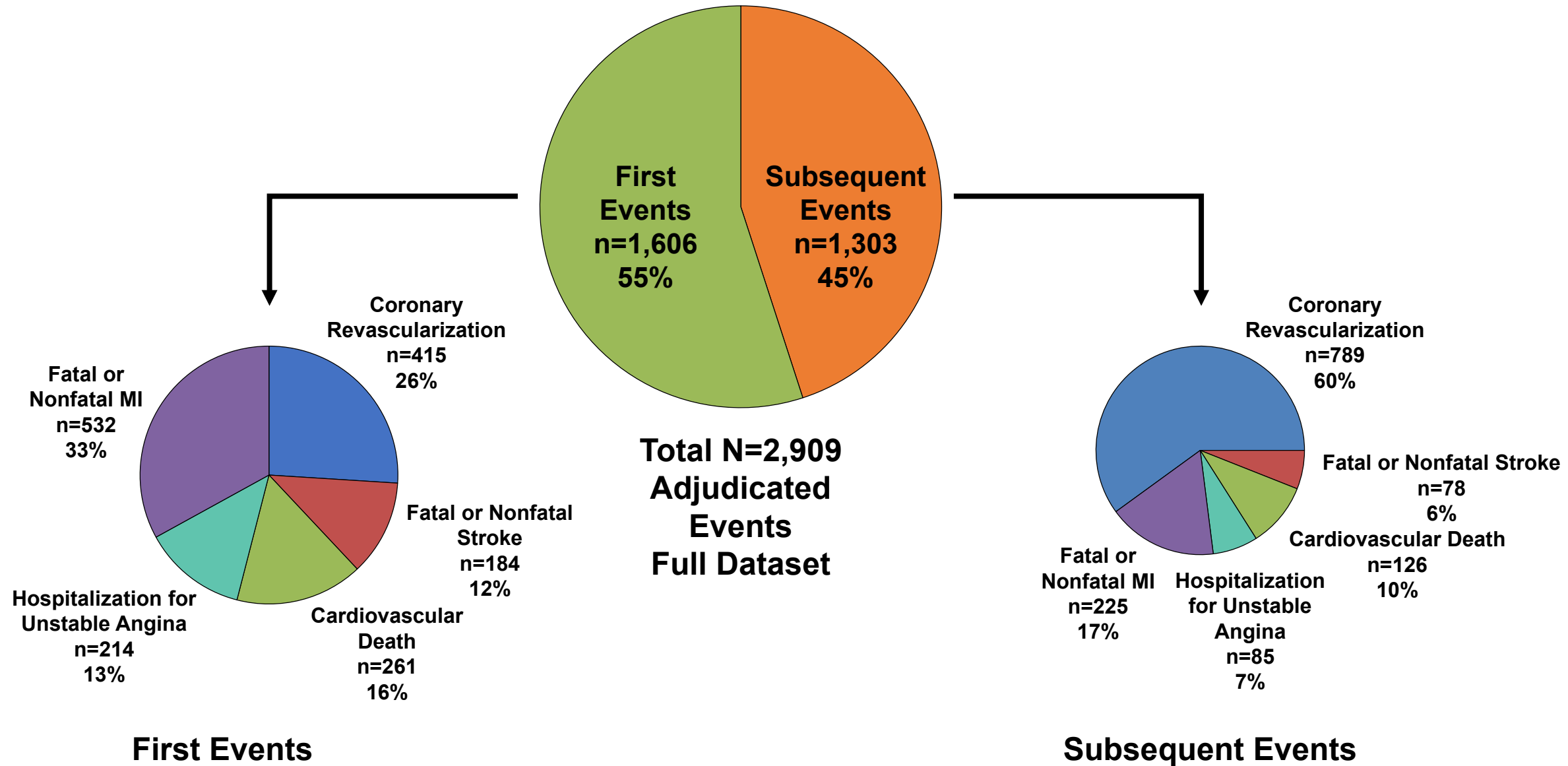


# Proportions of First and Subsequent Events





# Proportions of First and Subsequent Events



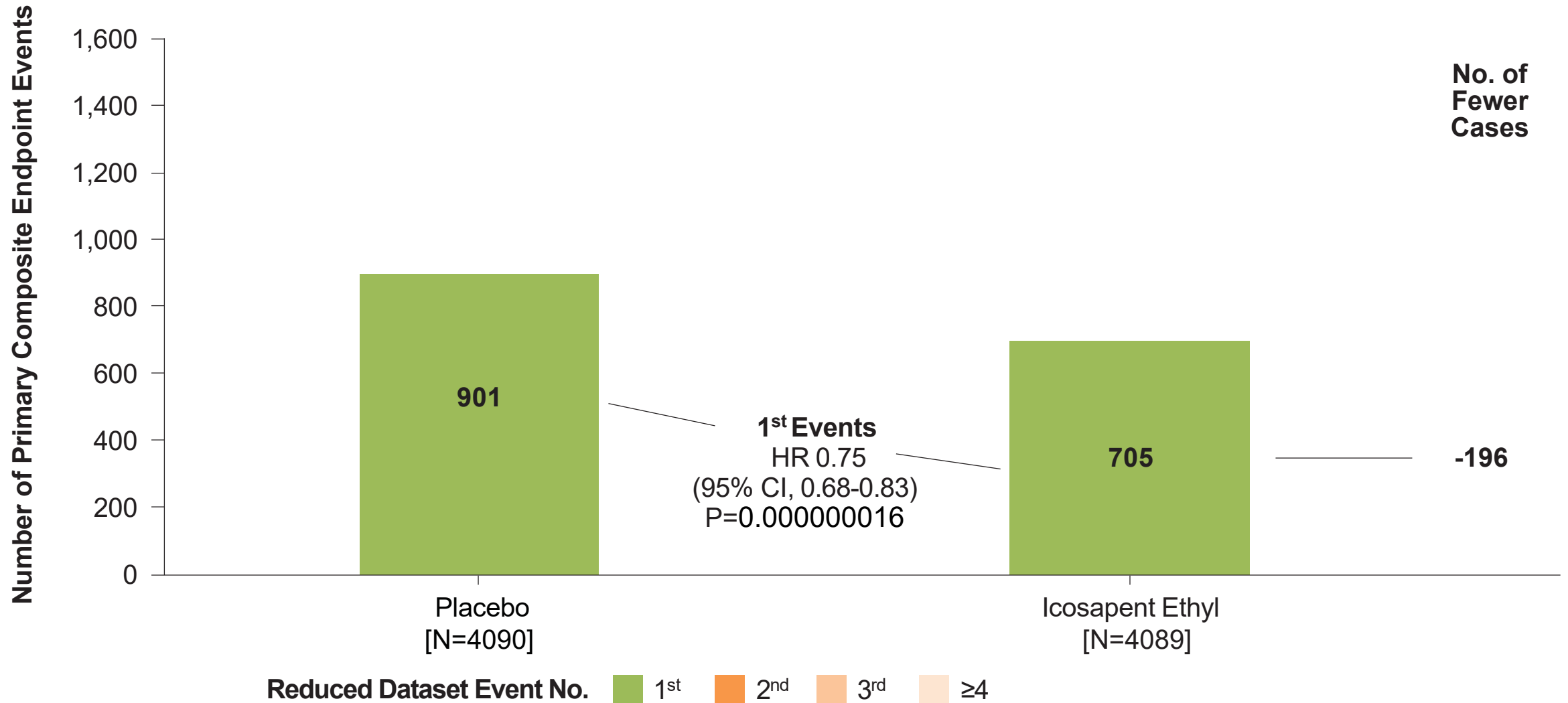
# Event Counts



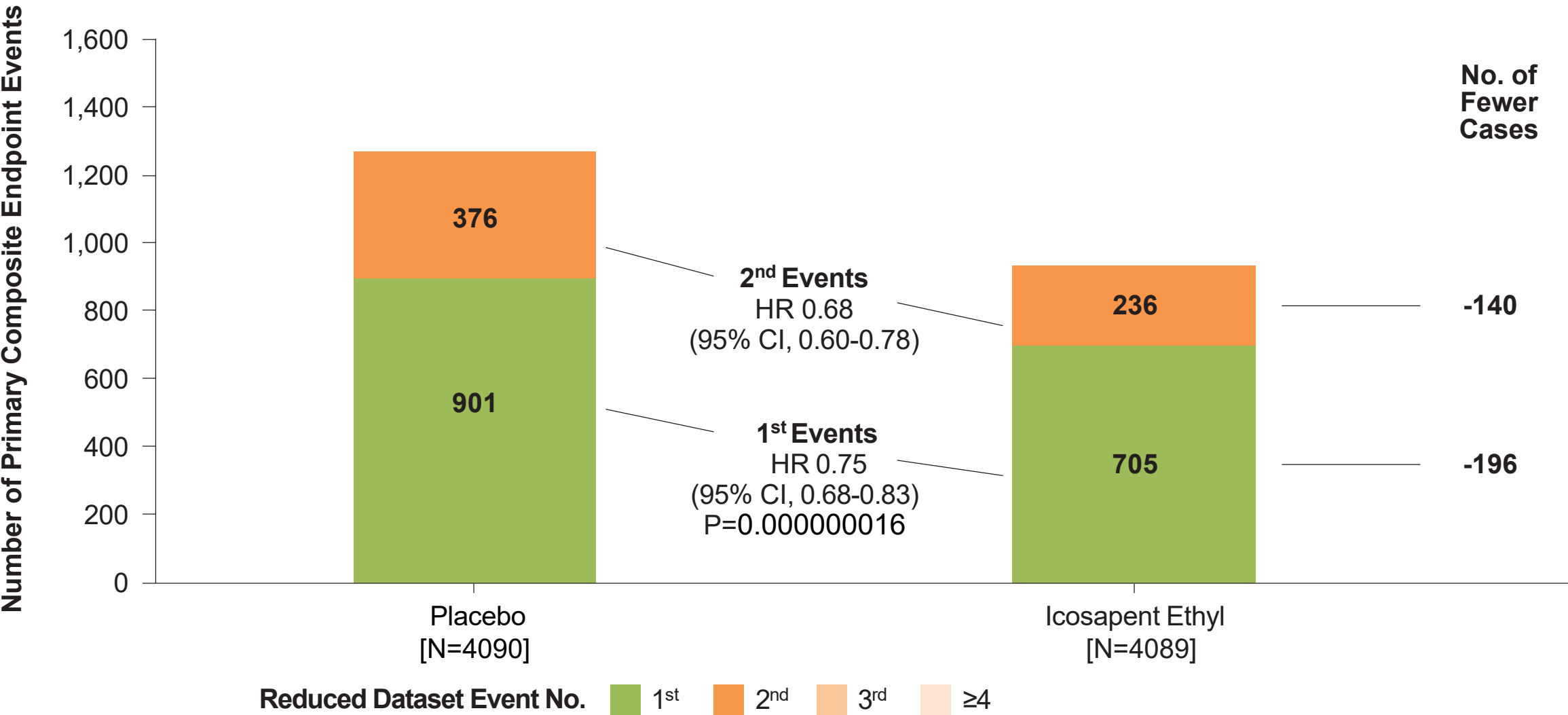
## Events on the Same Day:

- 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”

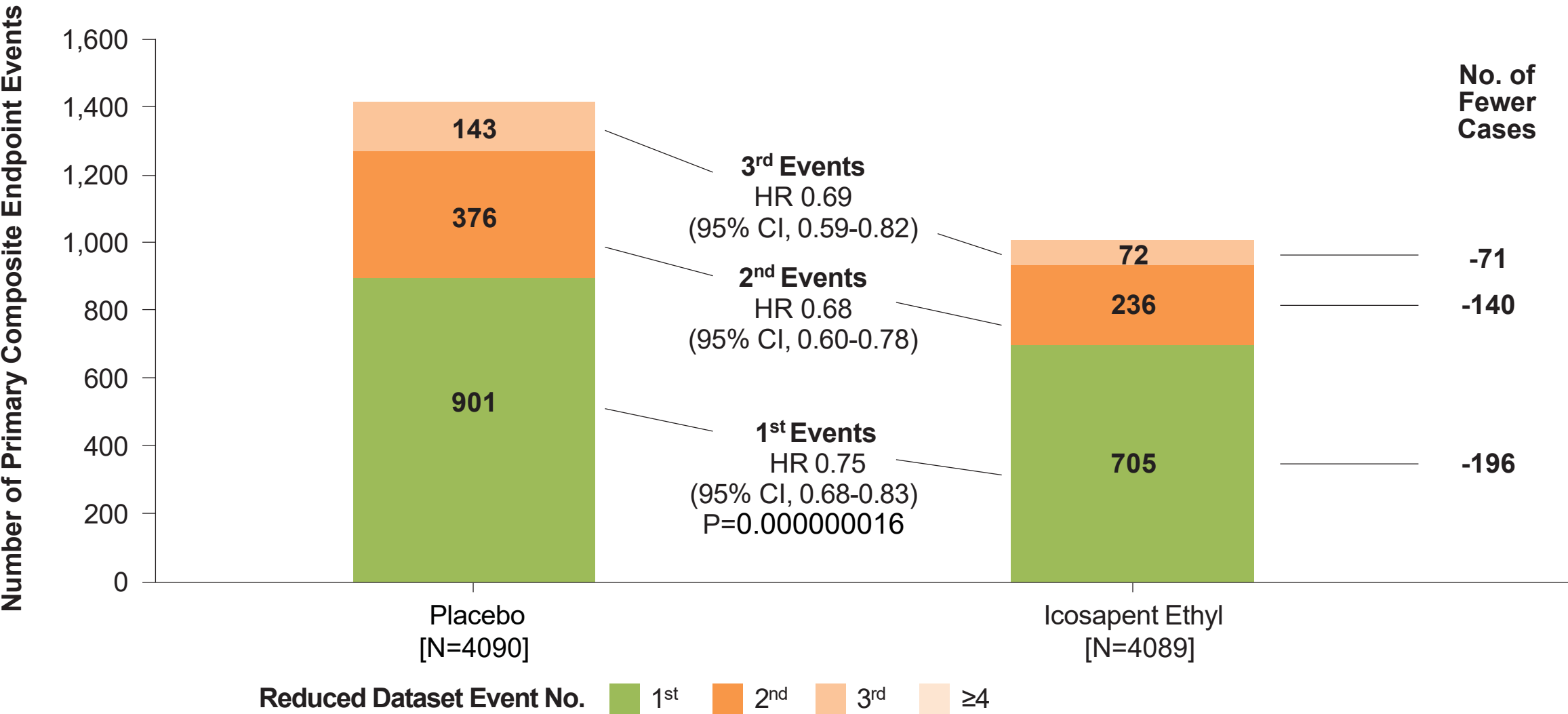
# First and Subsequent Events



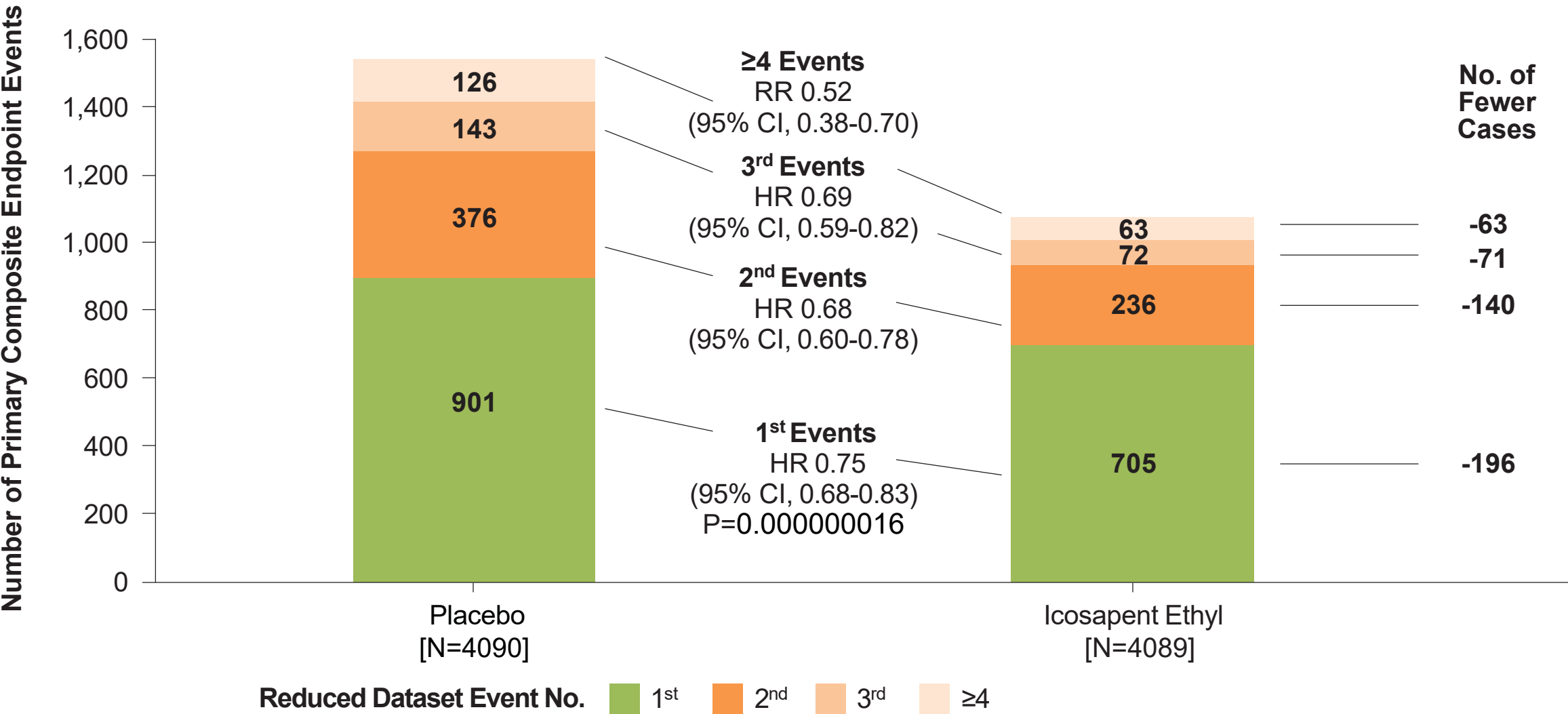
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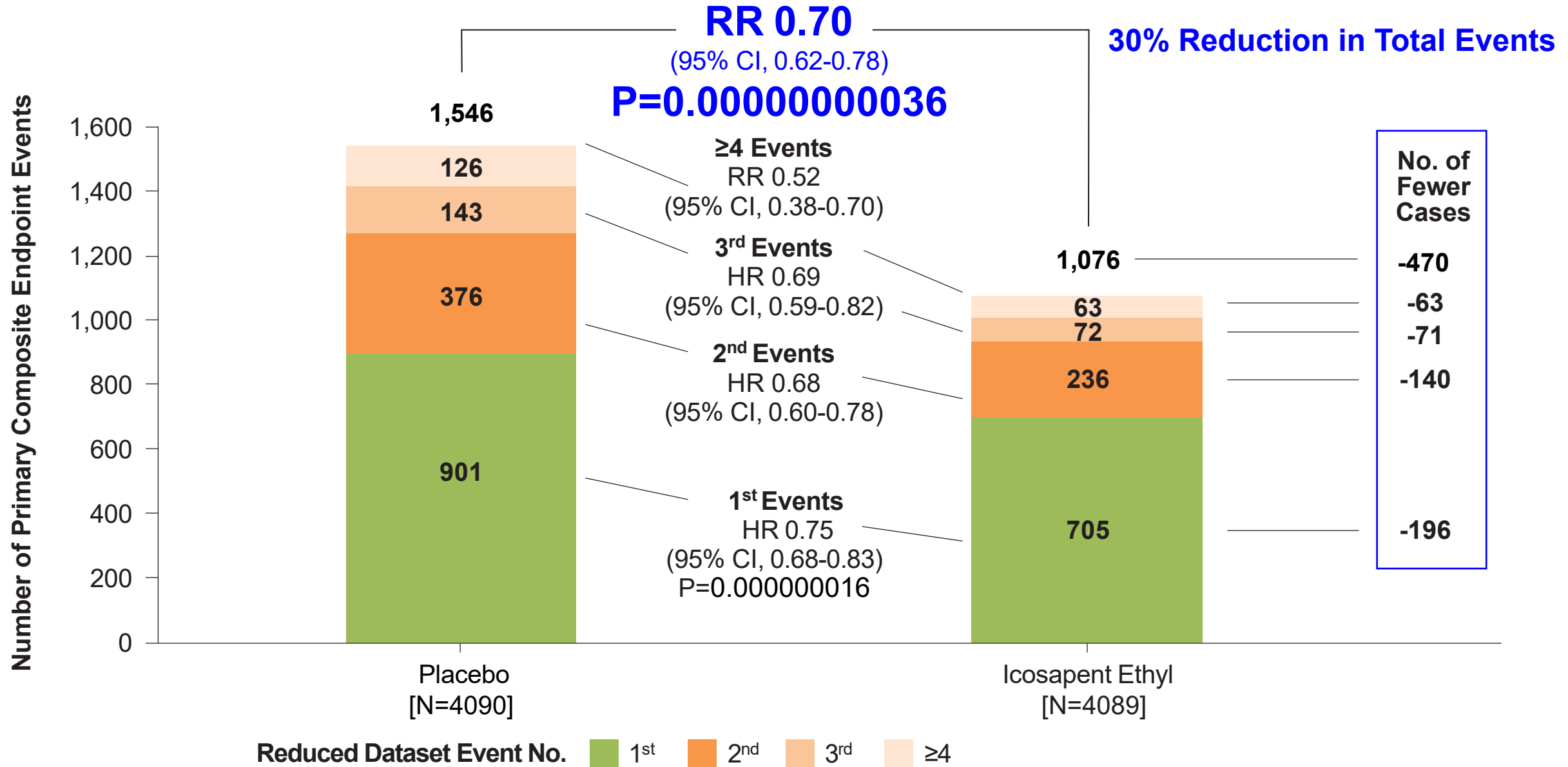
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# First and Subsequent Events



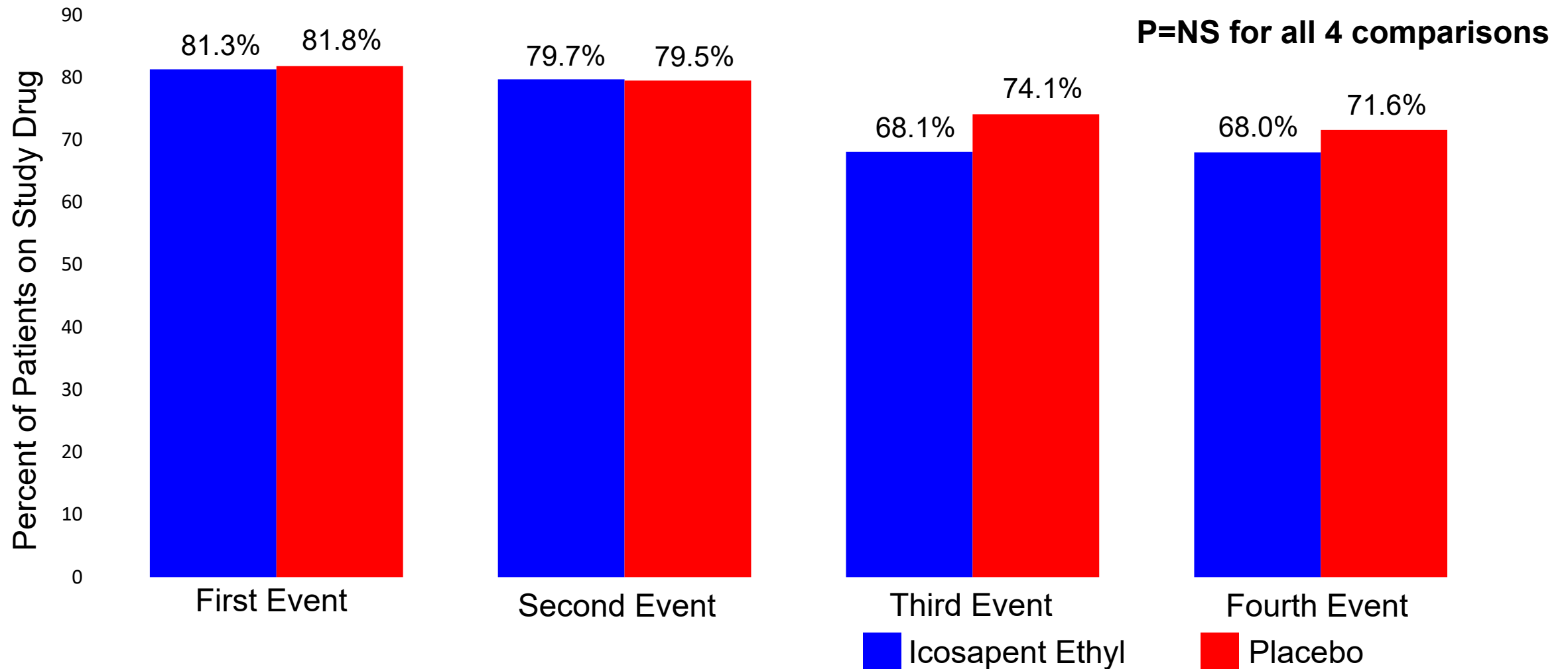
# First and Subsequent Events



# 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



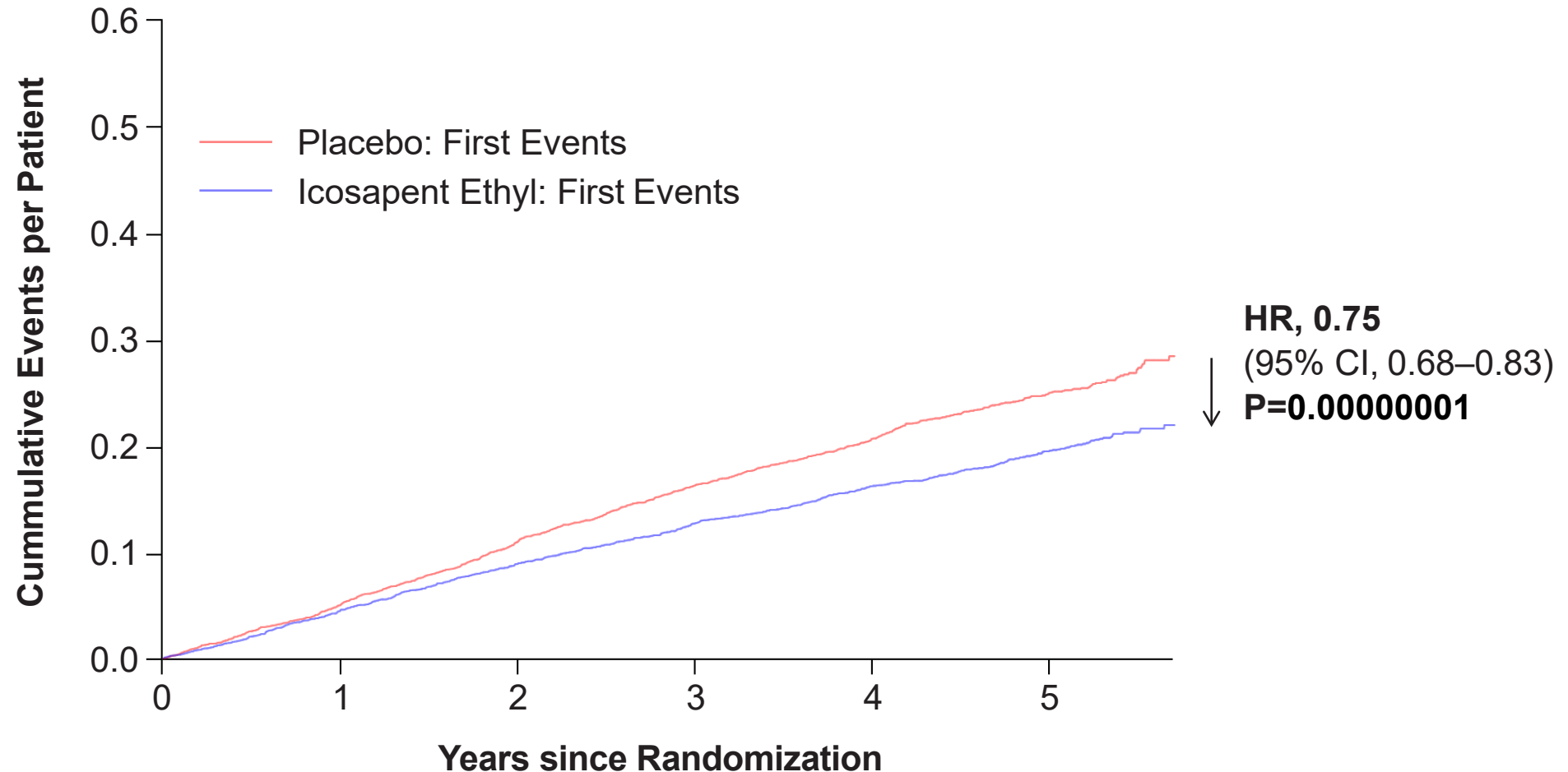


# Total (First and Subsequent) Events



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

Primary Composite Endpoint

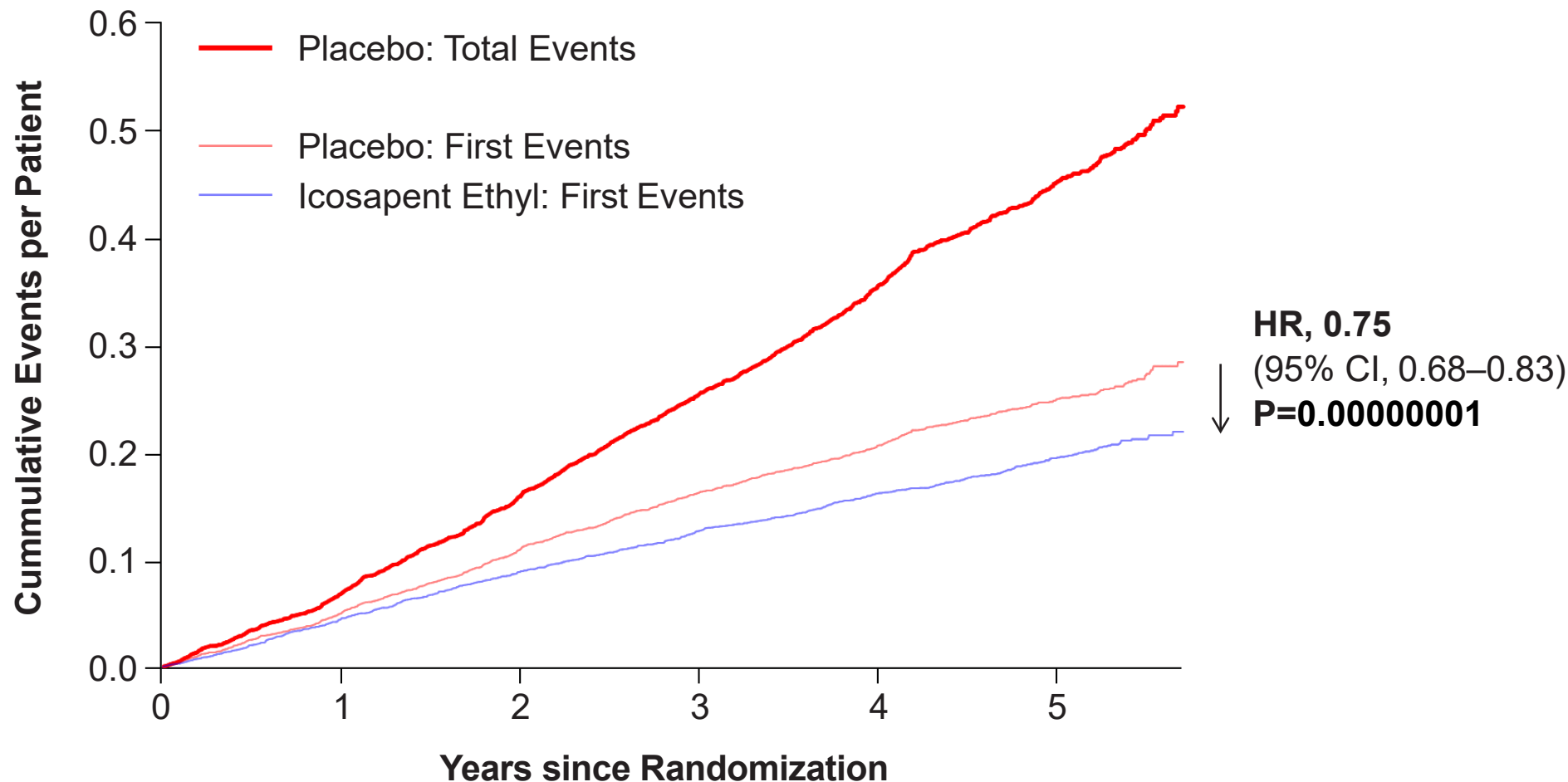


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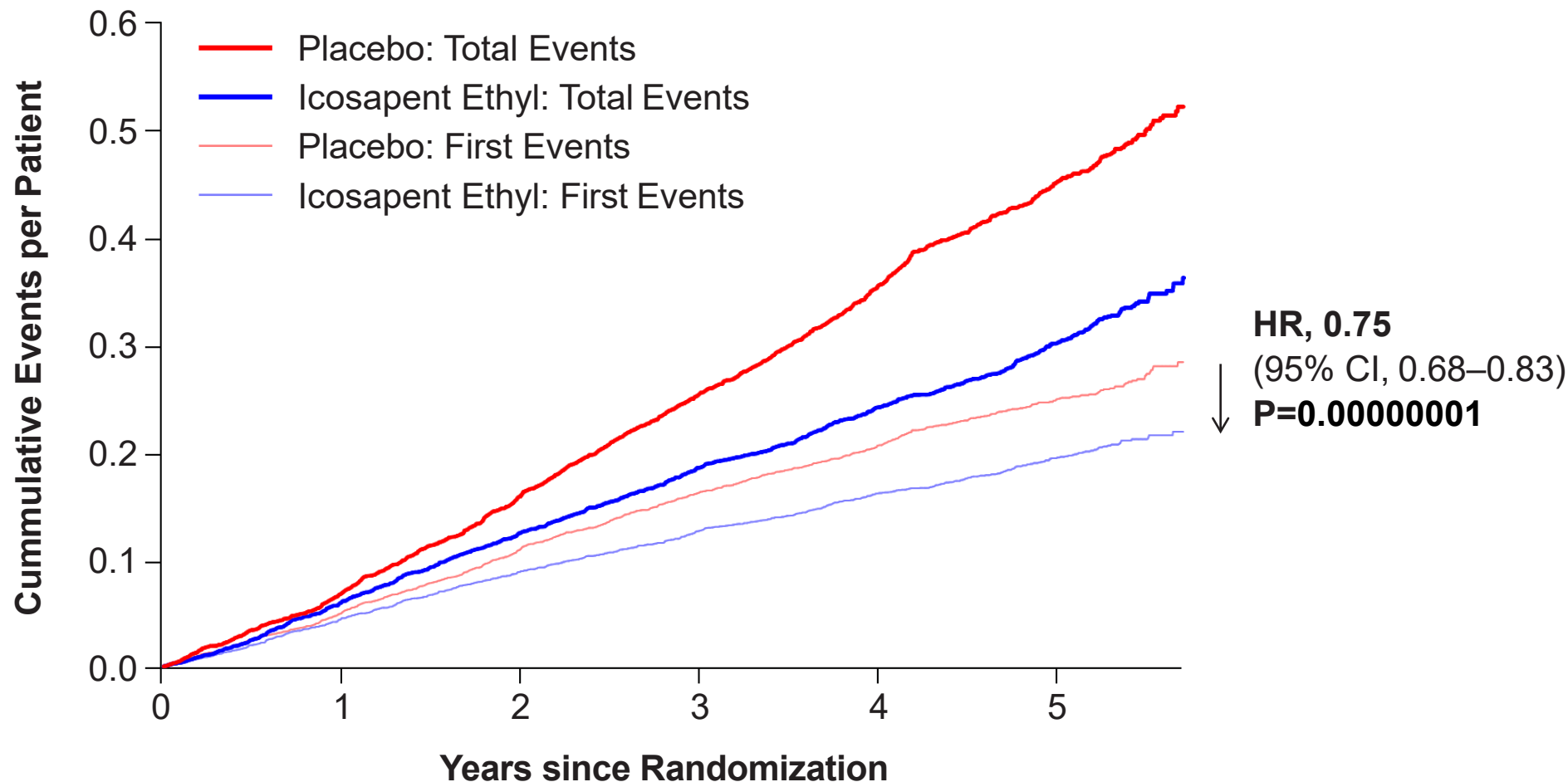


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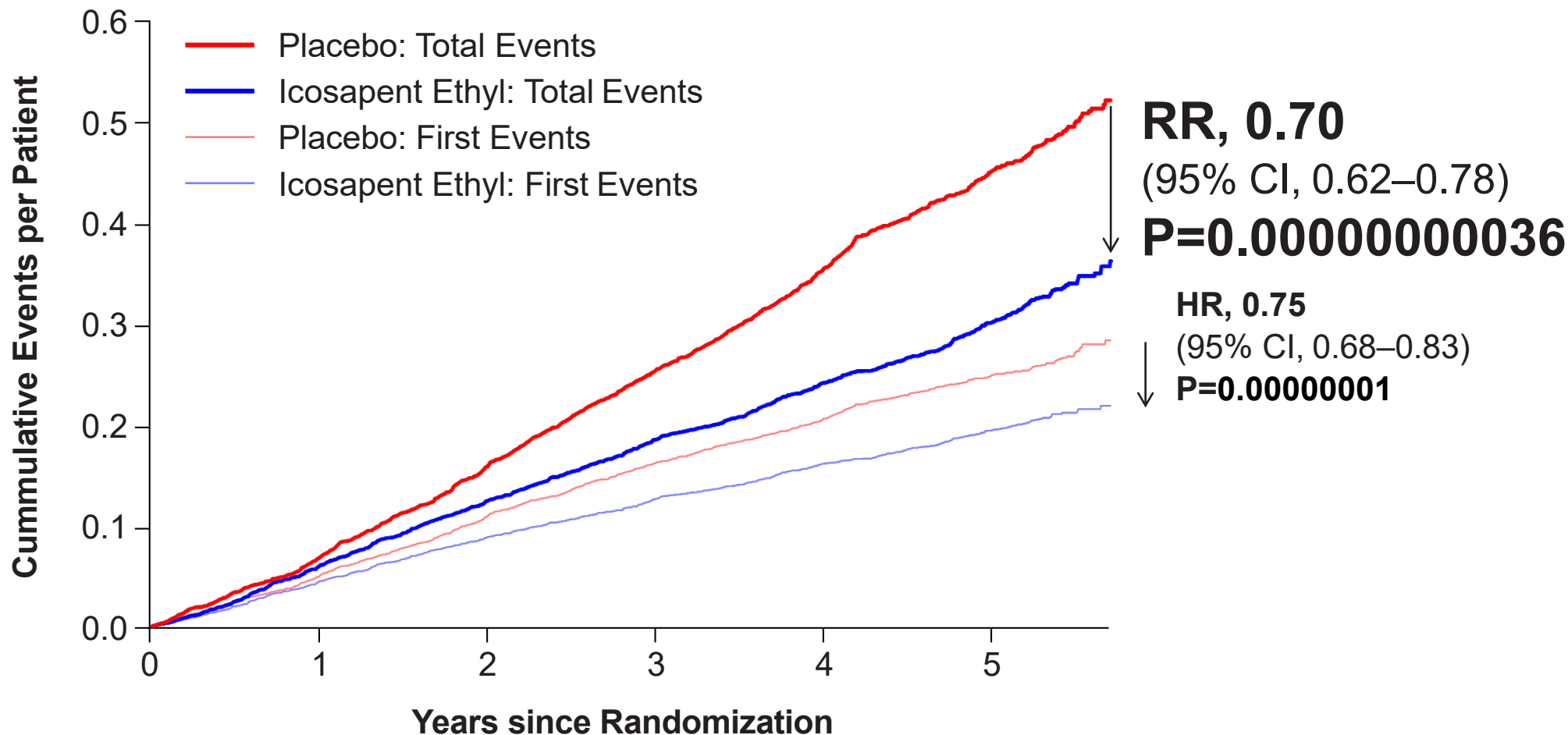


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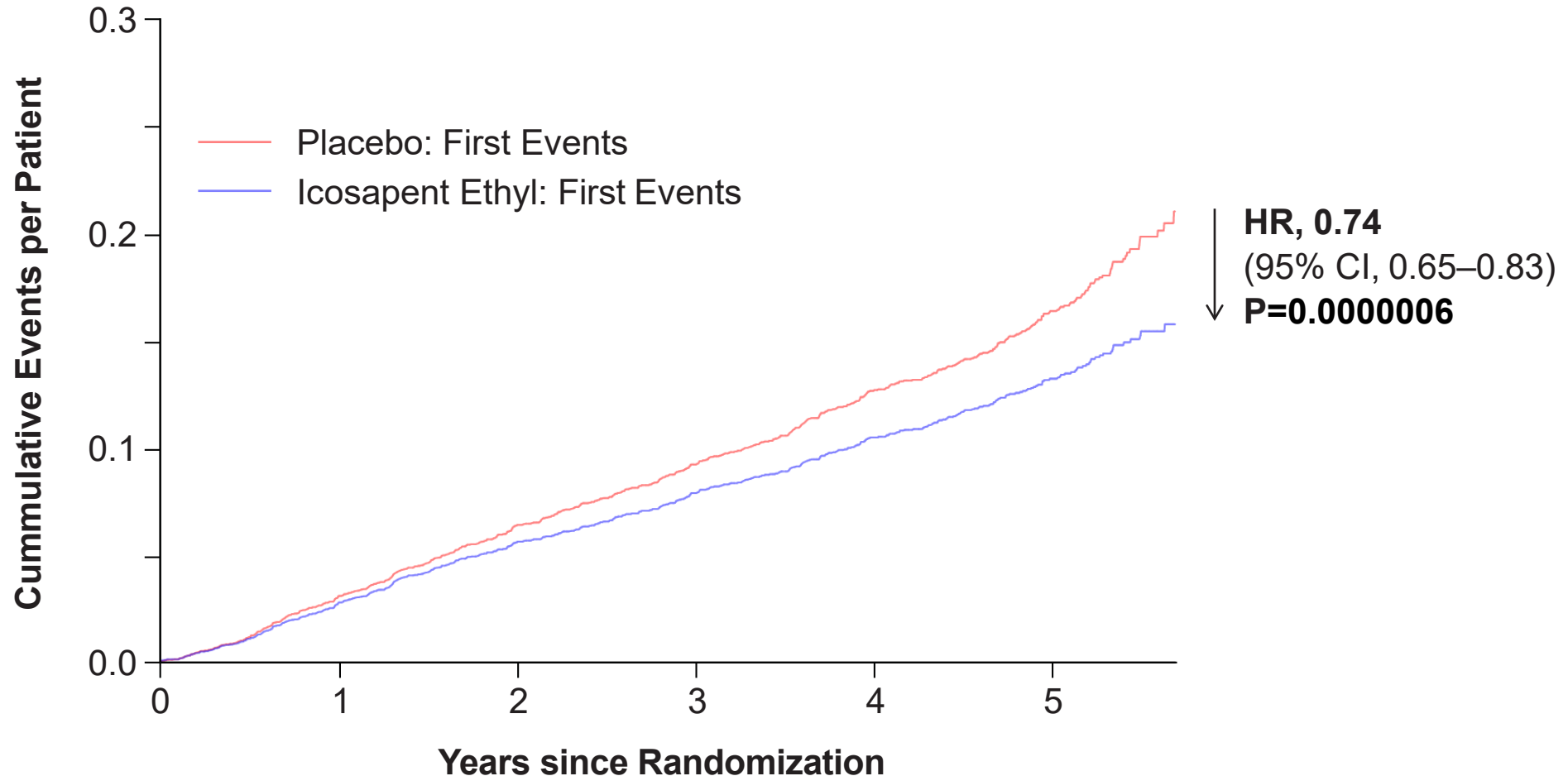


# Time to First Event

## Key Secondary: CV Death, MI, Stroke



Key Secondary Composite Endpoint

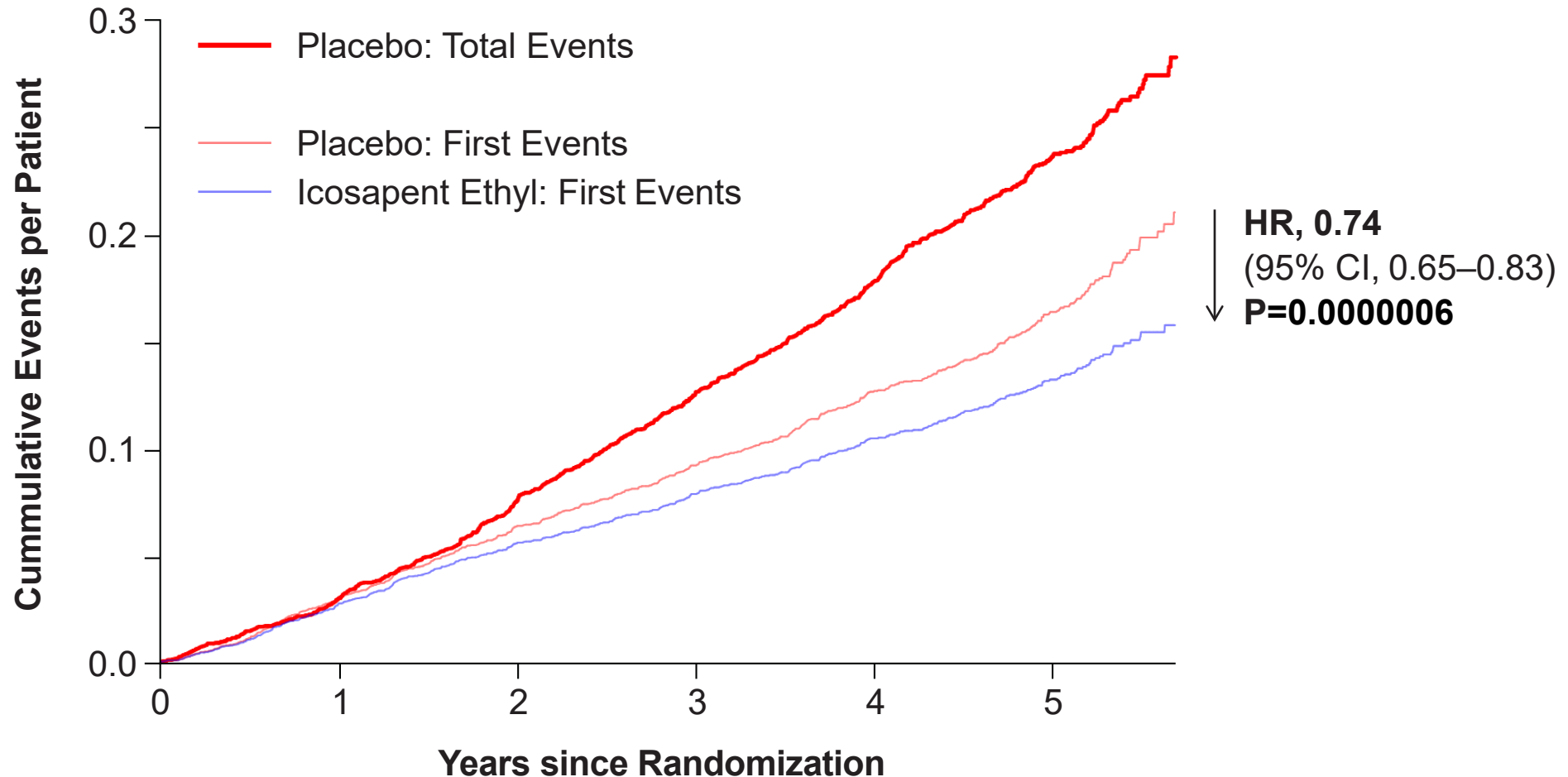


# Total (First and Subsequent) Events

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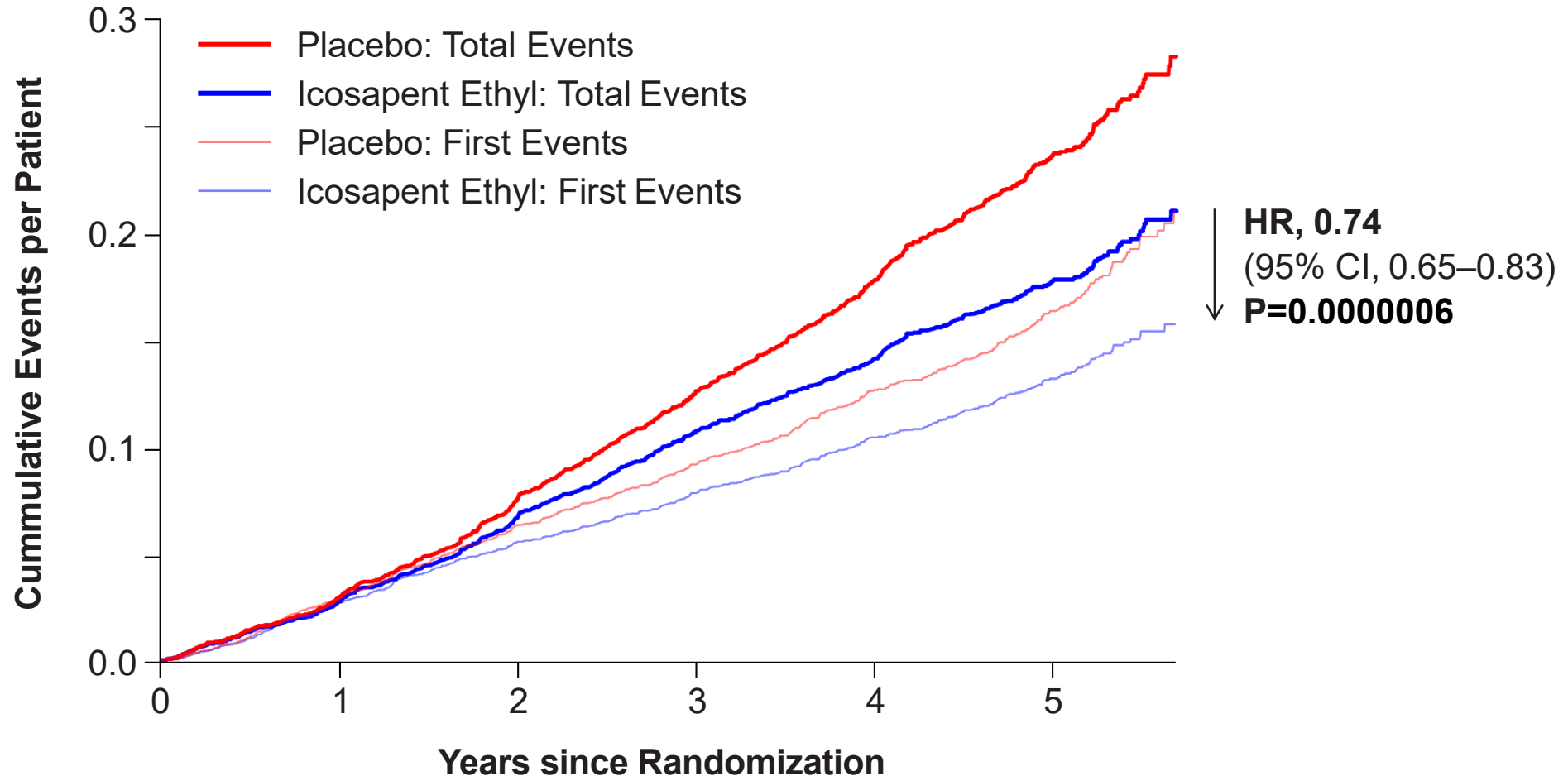


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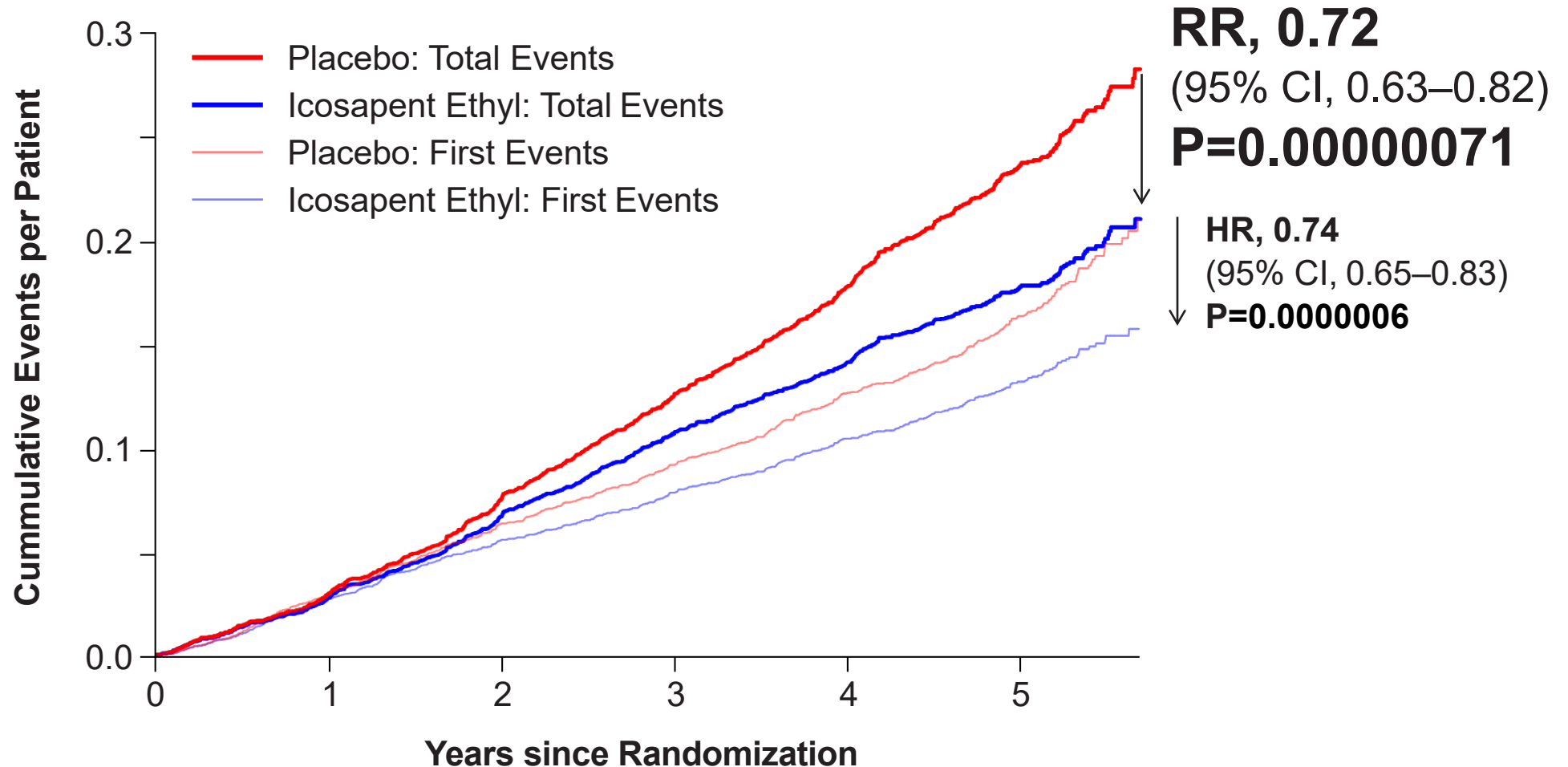


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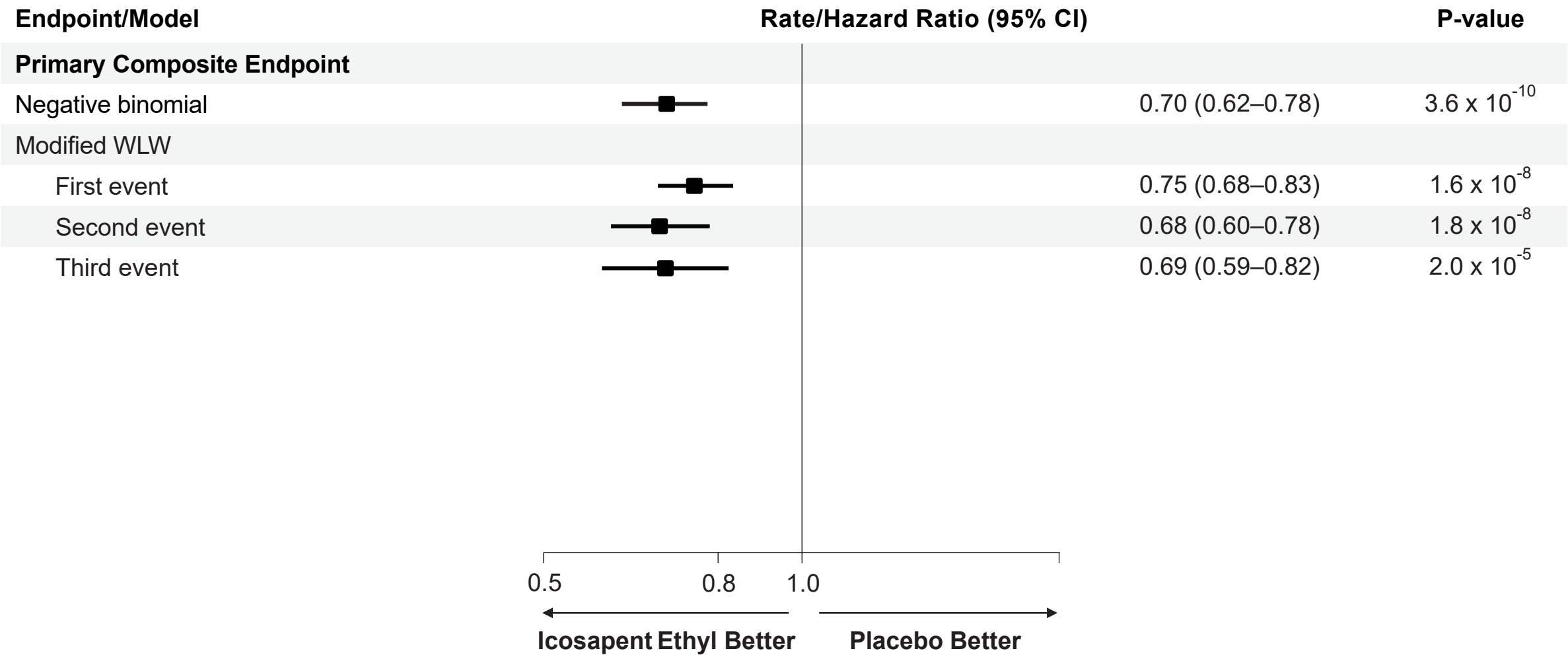


Key Secondary Composite Endpoint

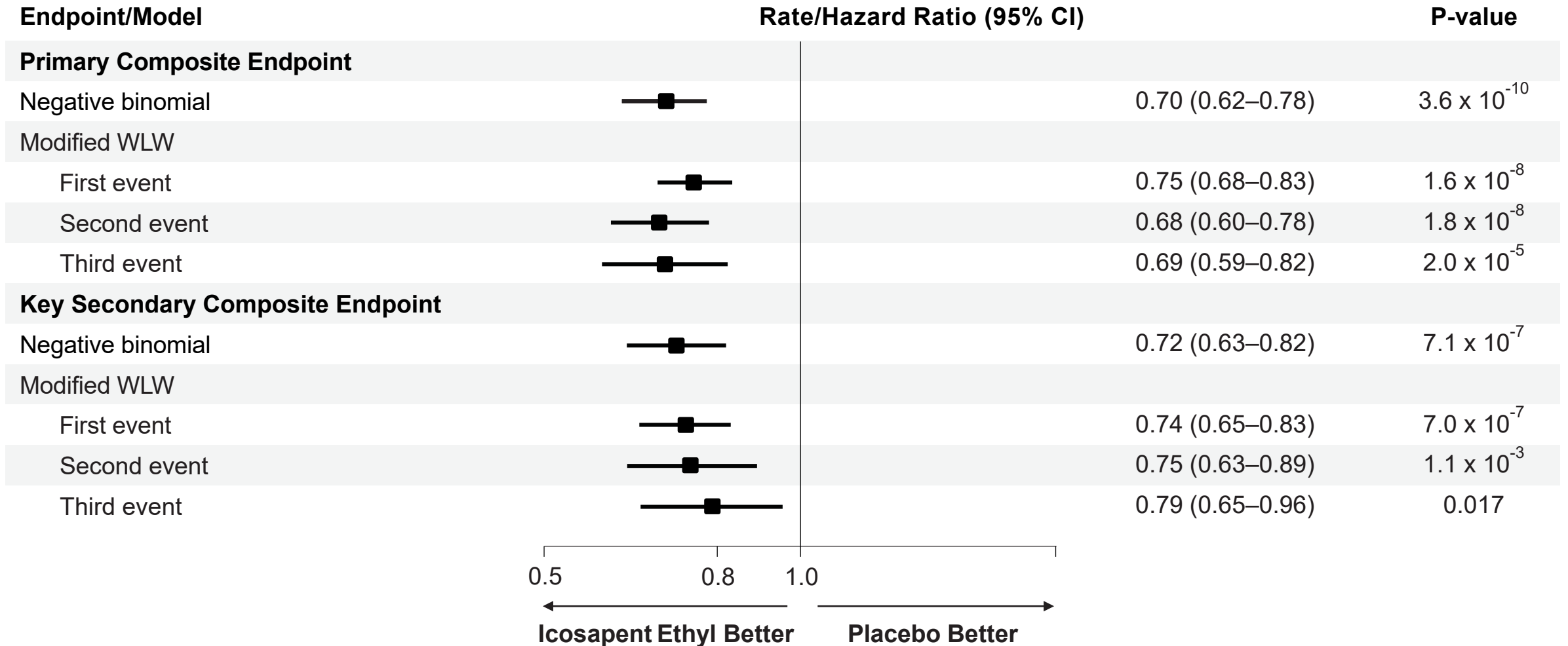




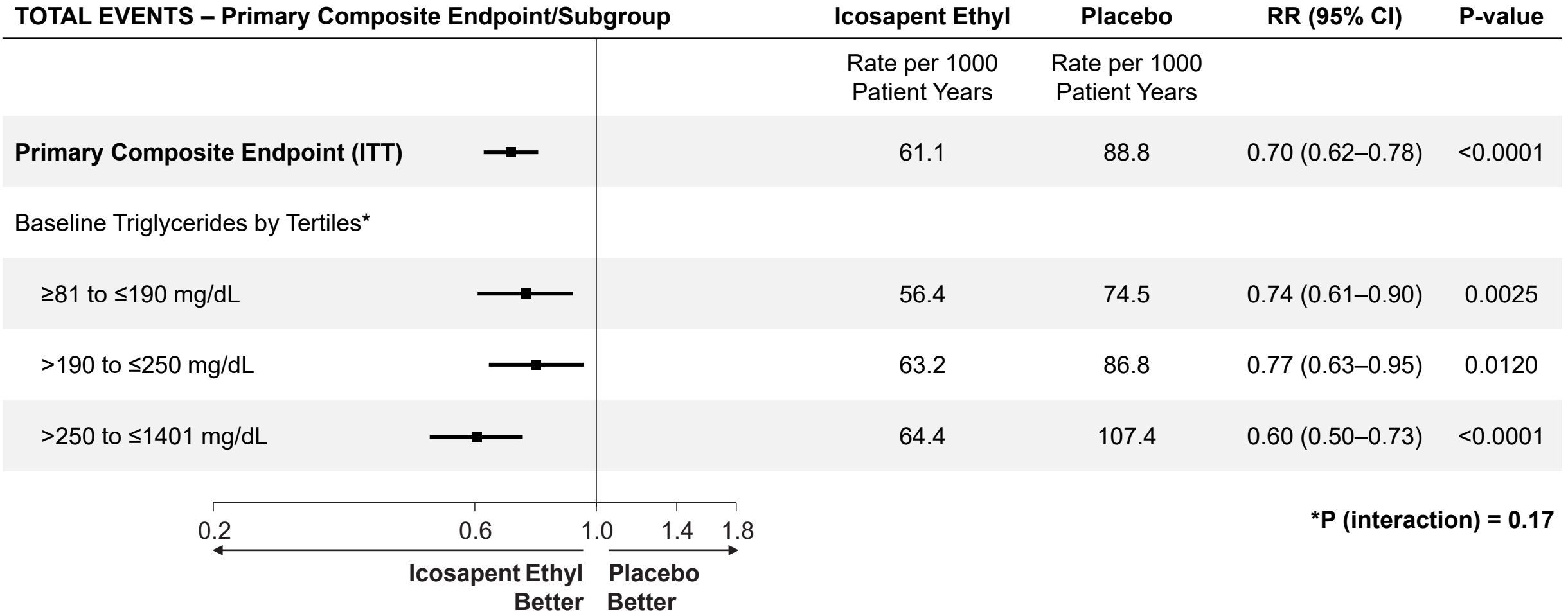
# Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences



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



# Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles



# 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:

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# Conclusions



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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
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- **48%** reduction in fourth or more cardiovascular events

# Conclusions



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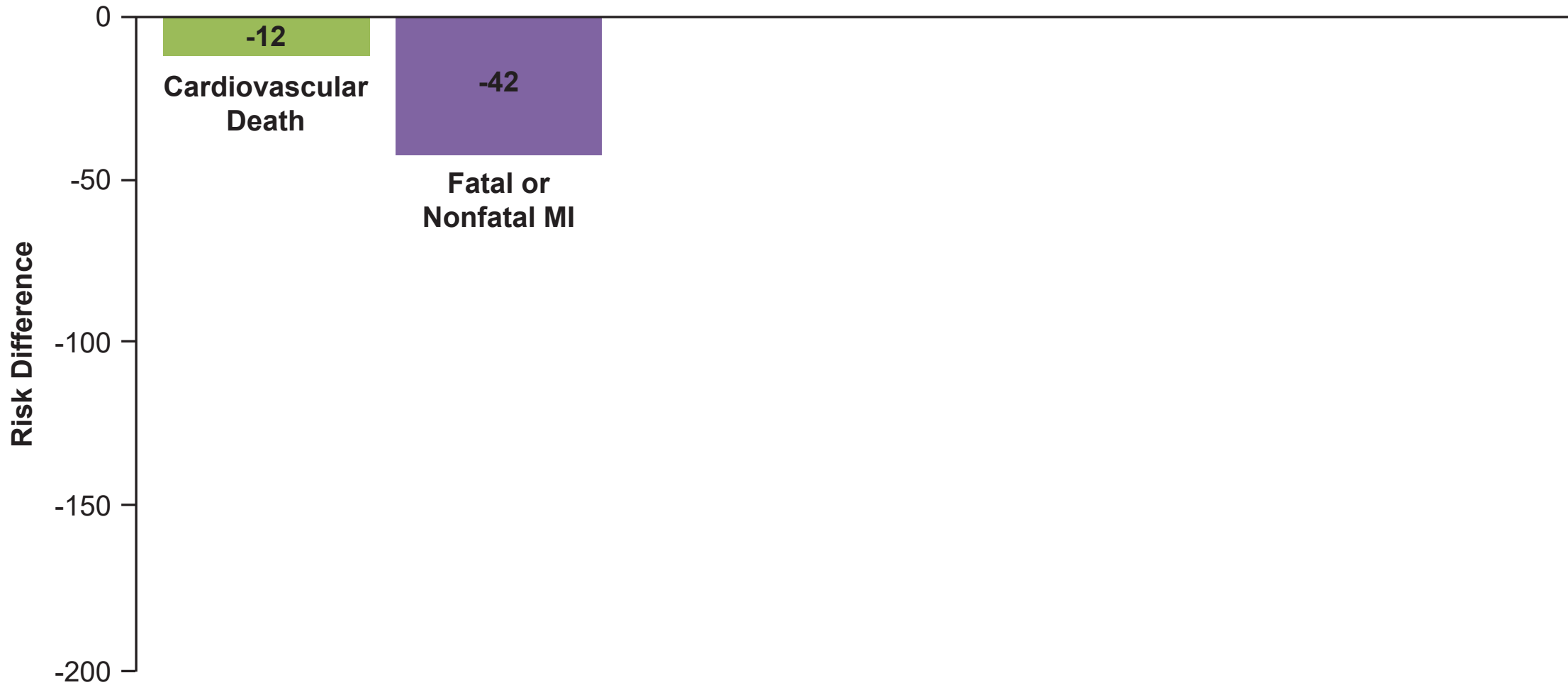
- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

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

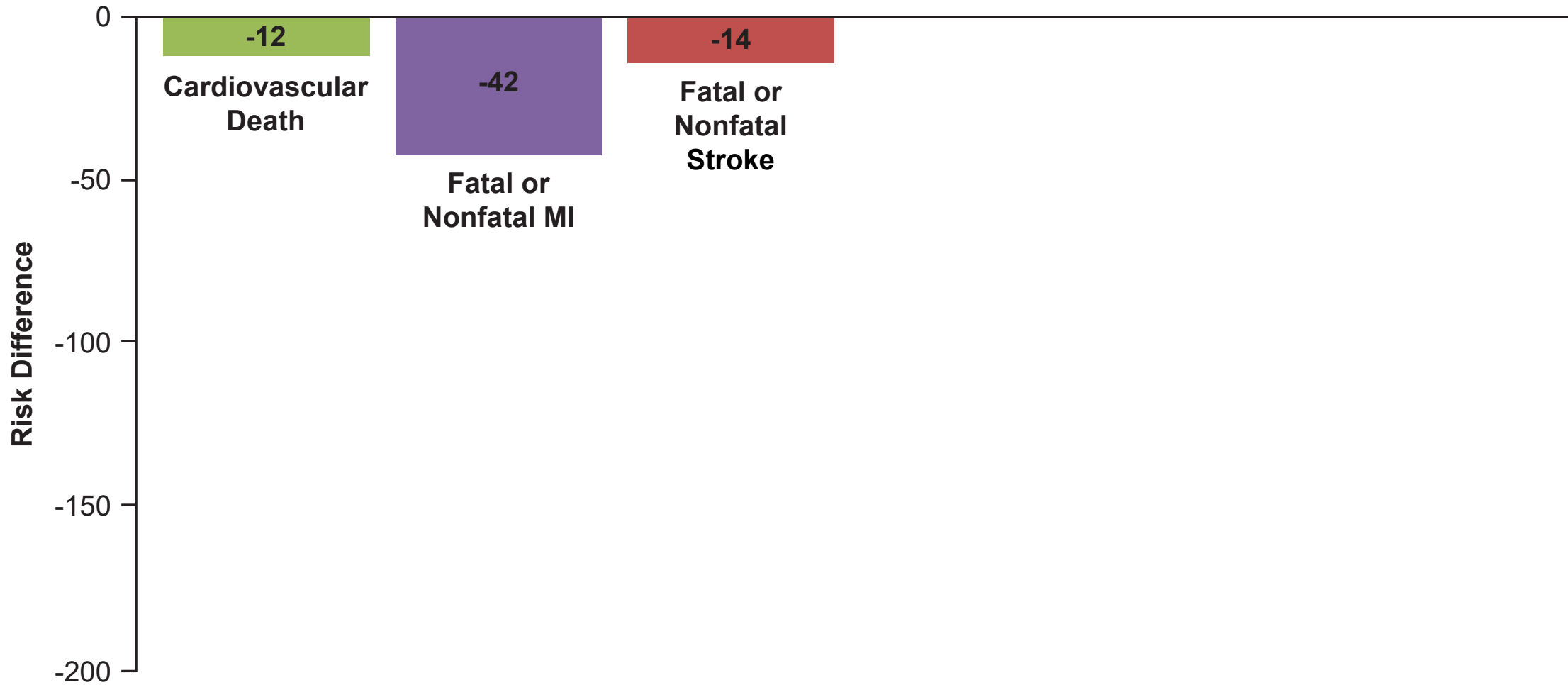
# For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:



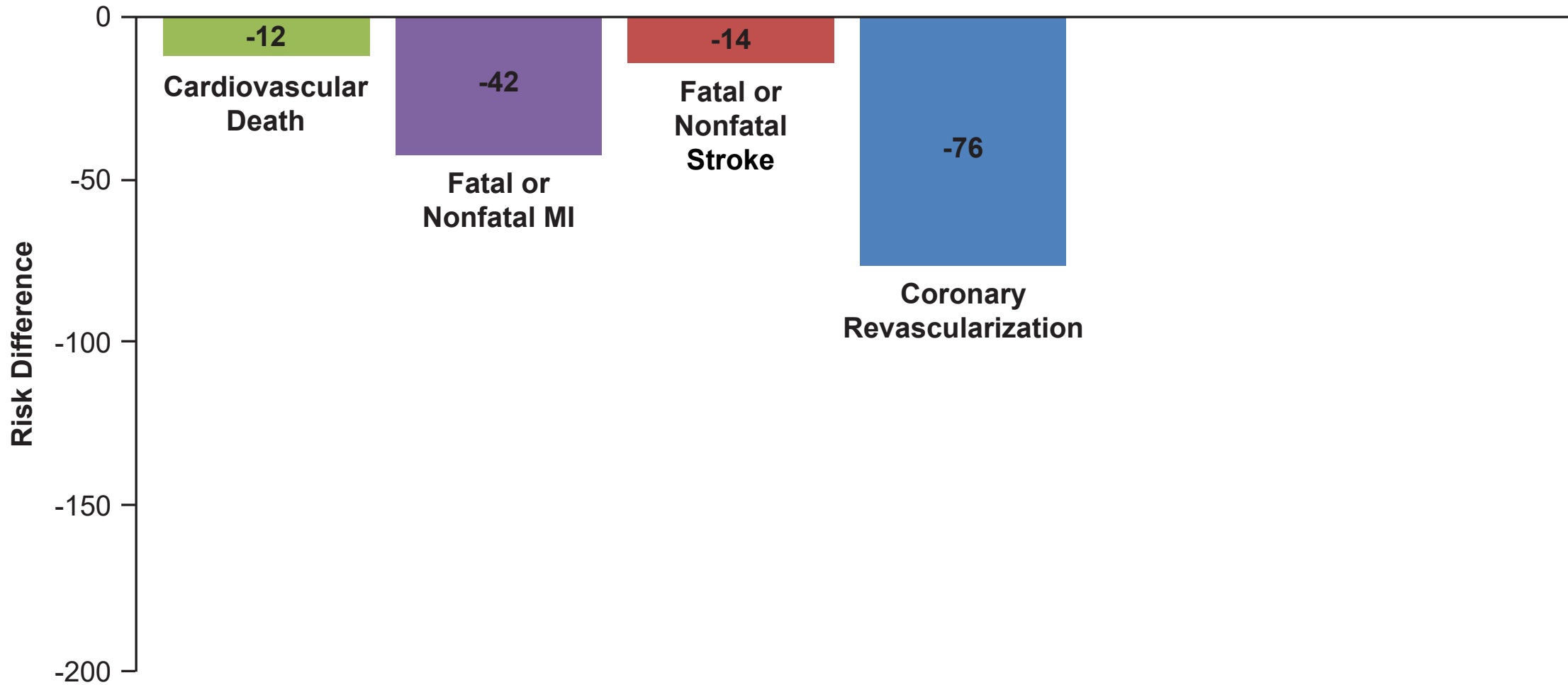
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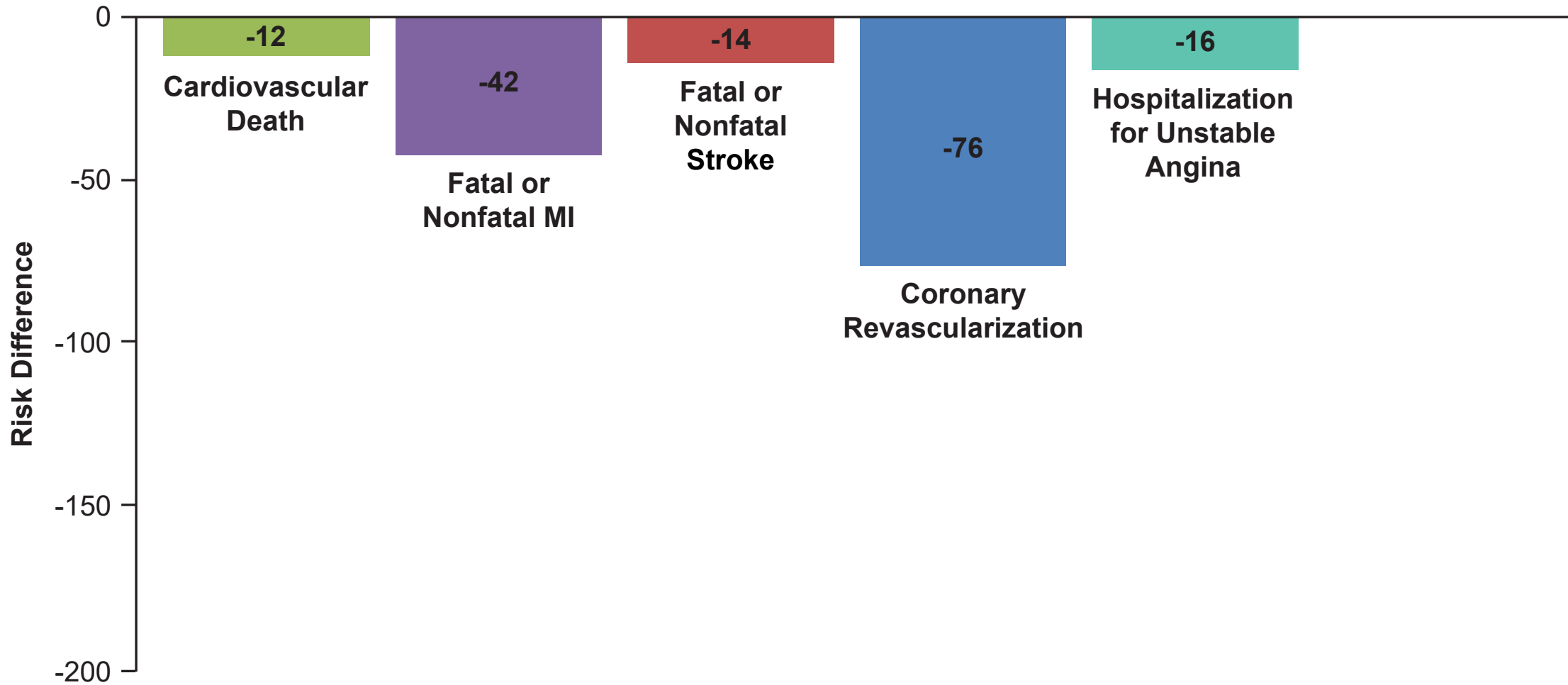
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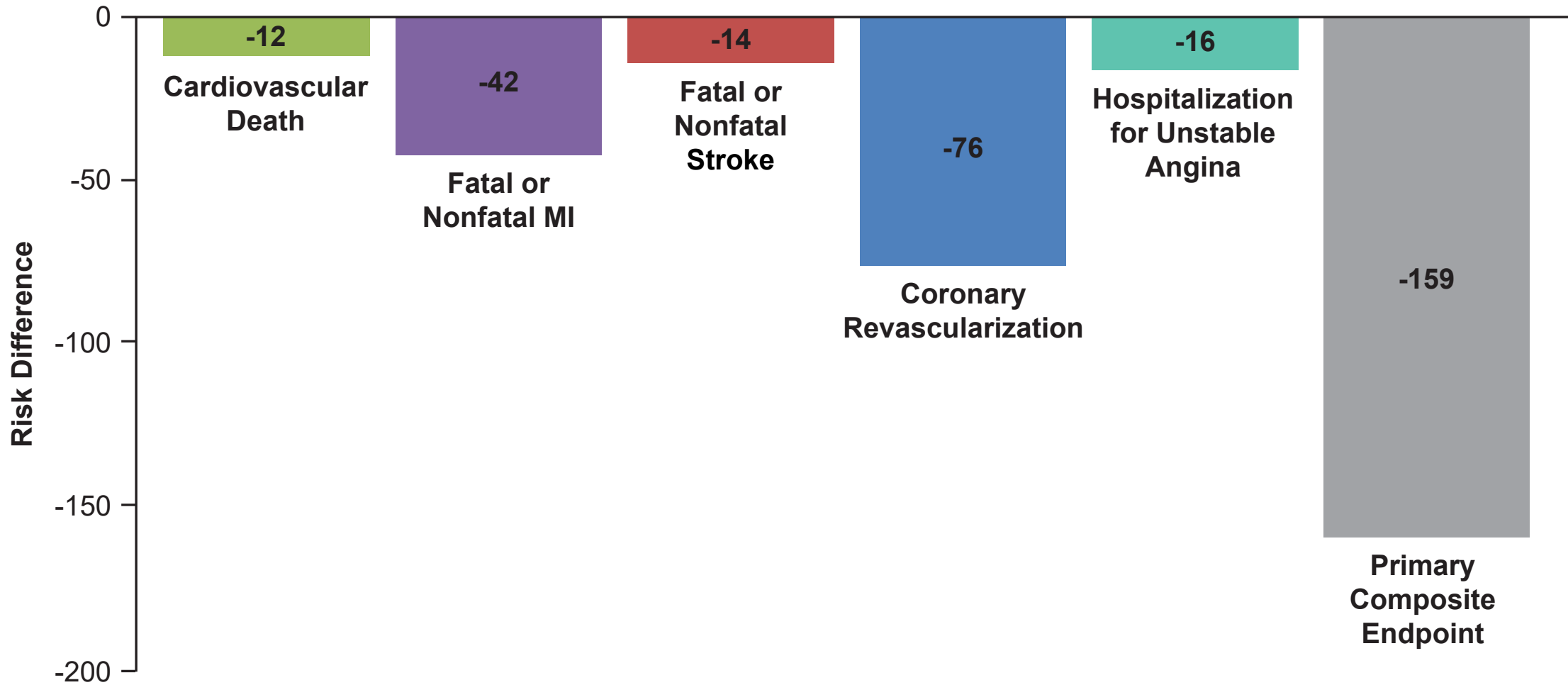
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# For Every 1000 Patients Treated with Icosapent Ethyl for 5 Years:





# 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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Jean-Claude Tardif, MD,<sup>h</sup> John Gregson, PhD,<sup>i</sup> Stuart J. Pocock, PhD,<sup>i</sup> Christie M. Ballantyne, MD,<sup>j</sup> on Behalf of the  
REDUCE-IT Investigators\*

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>



# Baseline Triglyceride Levels



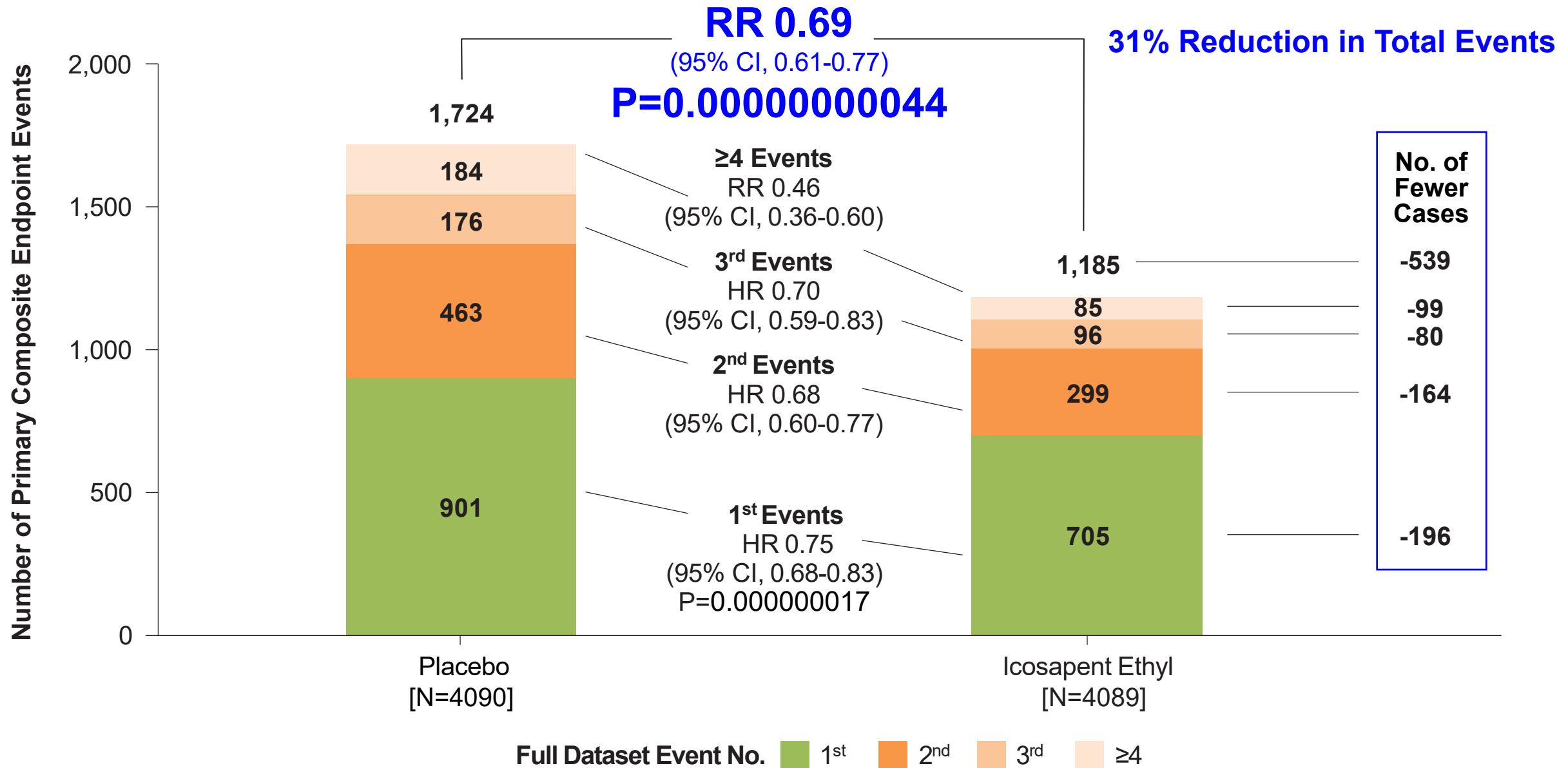
REDUCE-IT patients underwent a screening visit to determine eligibility, including testing of statin-stabilized triglyceride (TG) levels. Patients meeting inclusion and exclusion criteria, including TG levels could then be entered in the study at a subsequent randomization visit. Patients not meeting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

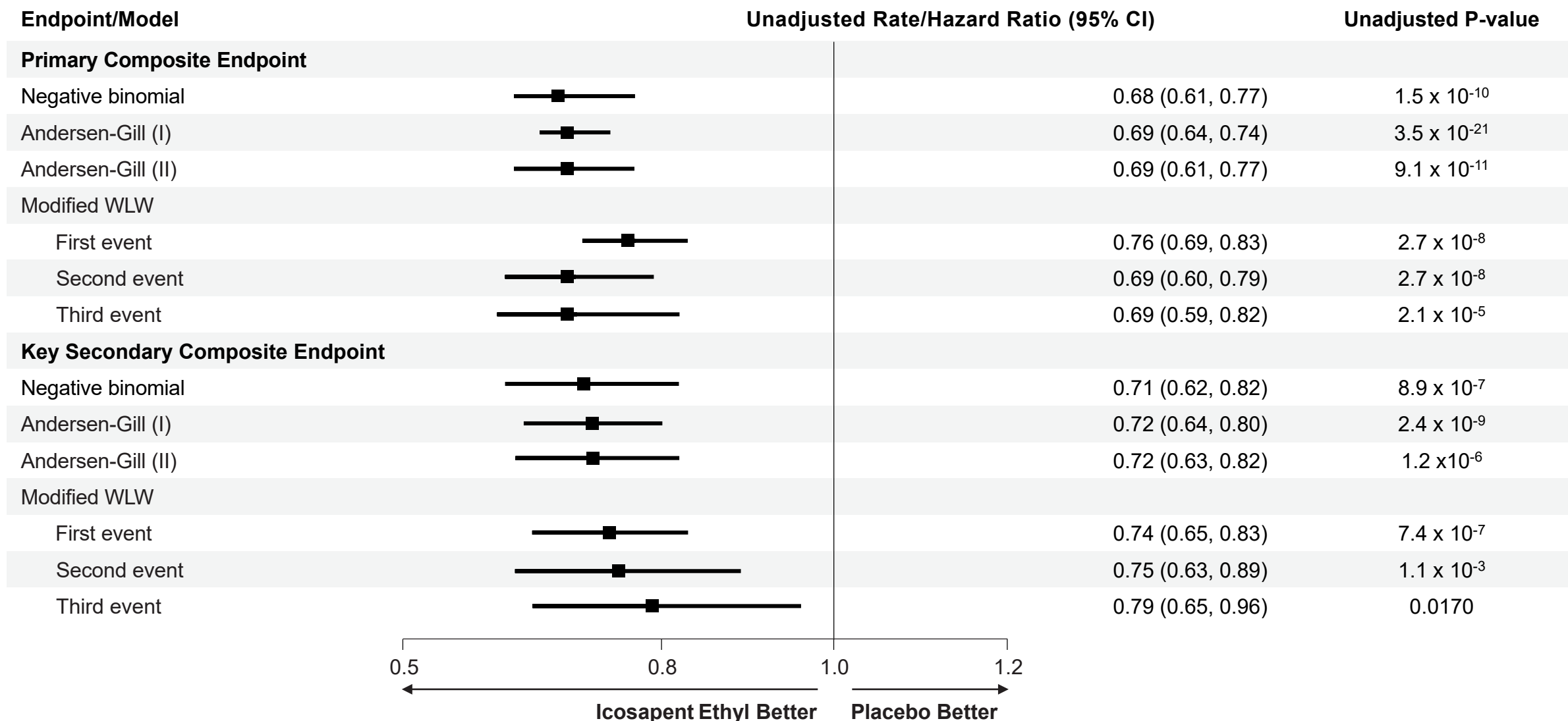
Each patient's baseline TG value was calculated as the average of the final screening TG and the subsequent TG value from date of randomization. Therefore, the baseline TG levels ranged from 81 mg/dL to 1401 mg/dL.

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

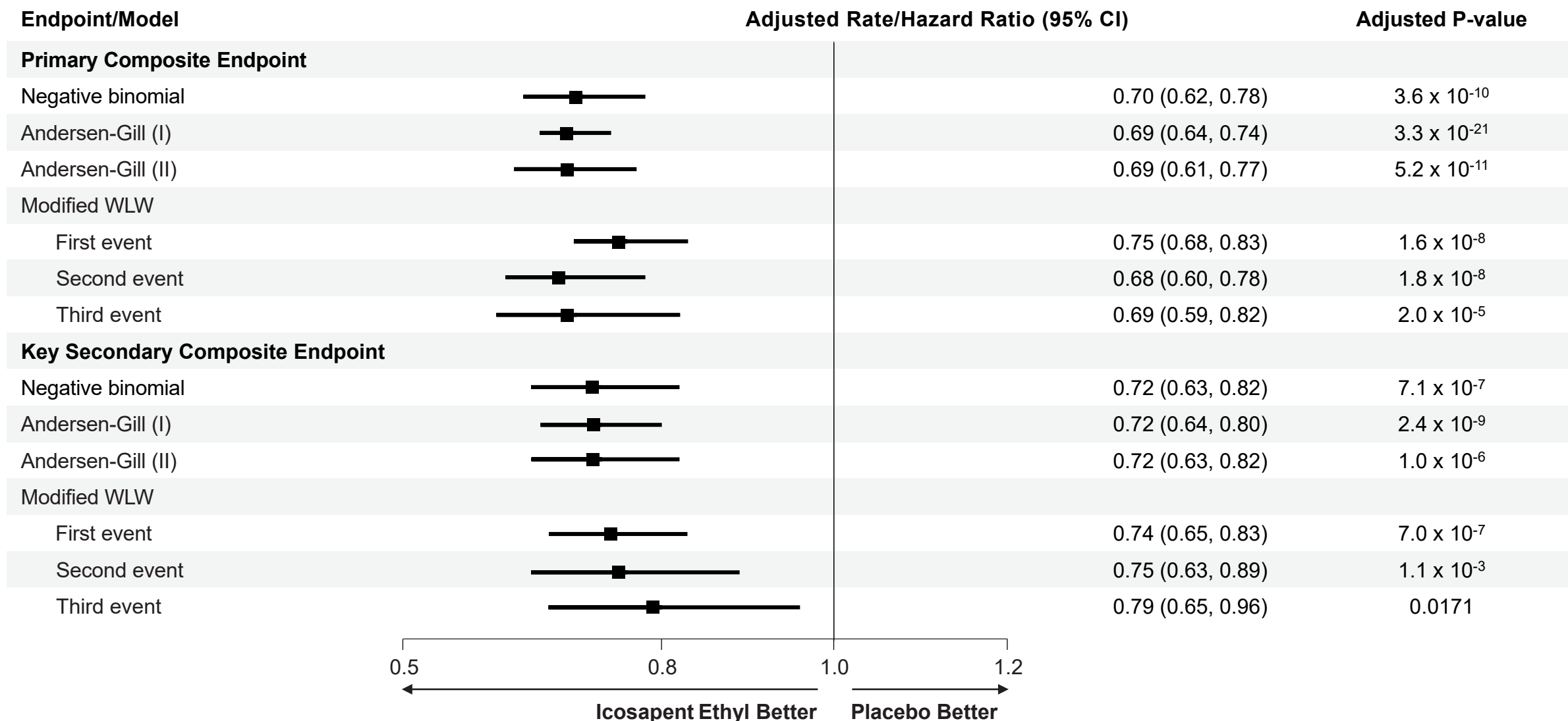
# Distribution of First and Subsequent Events



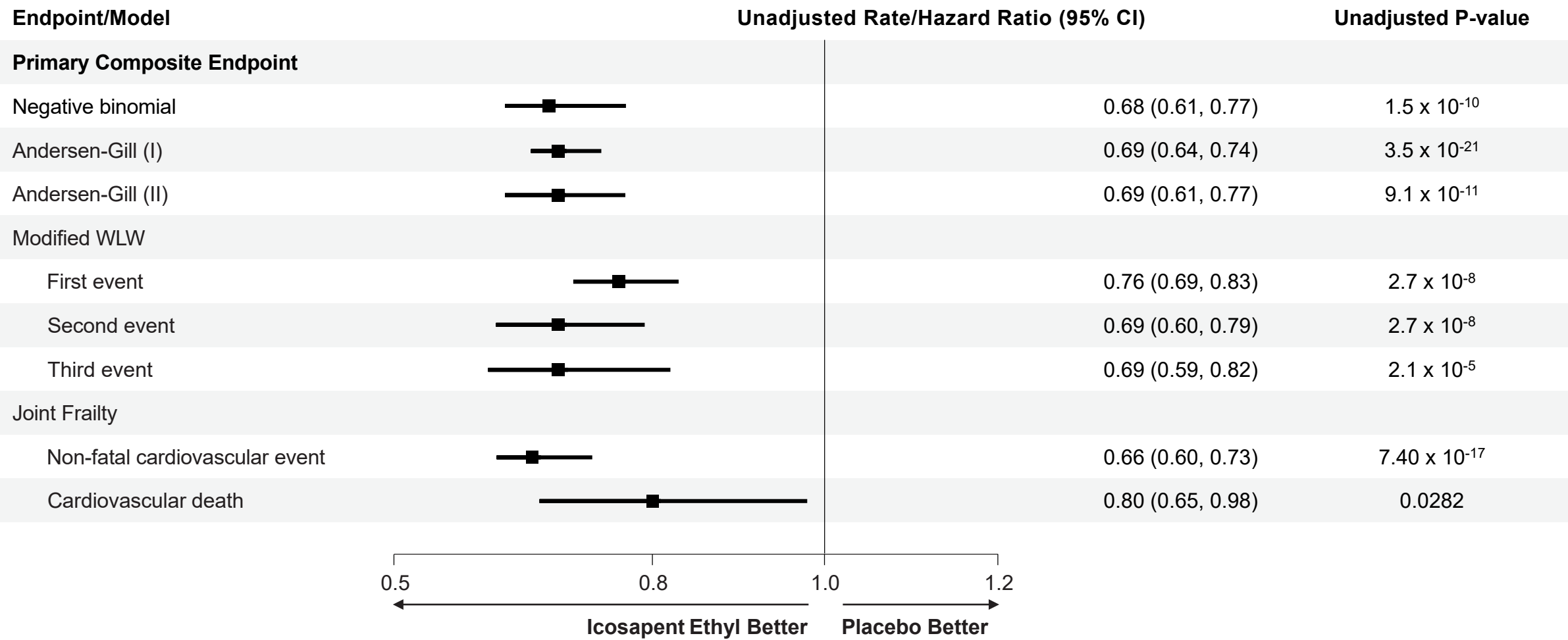
# Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Unadjusted)



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



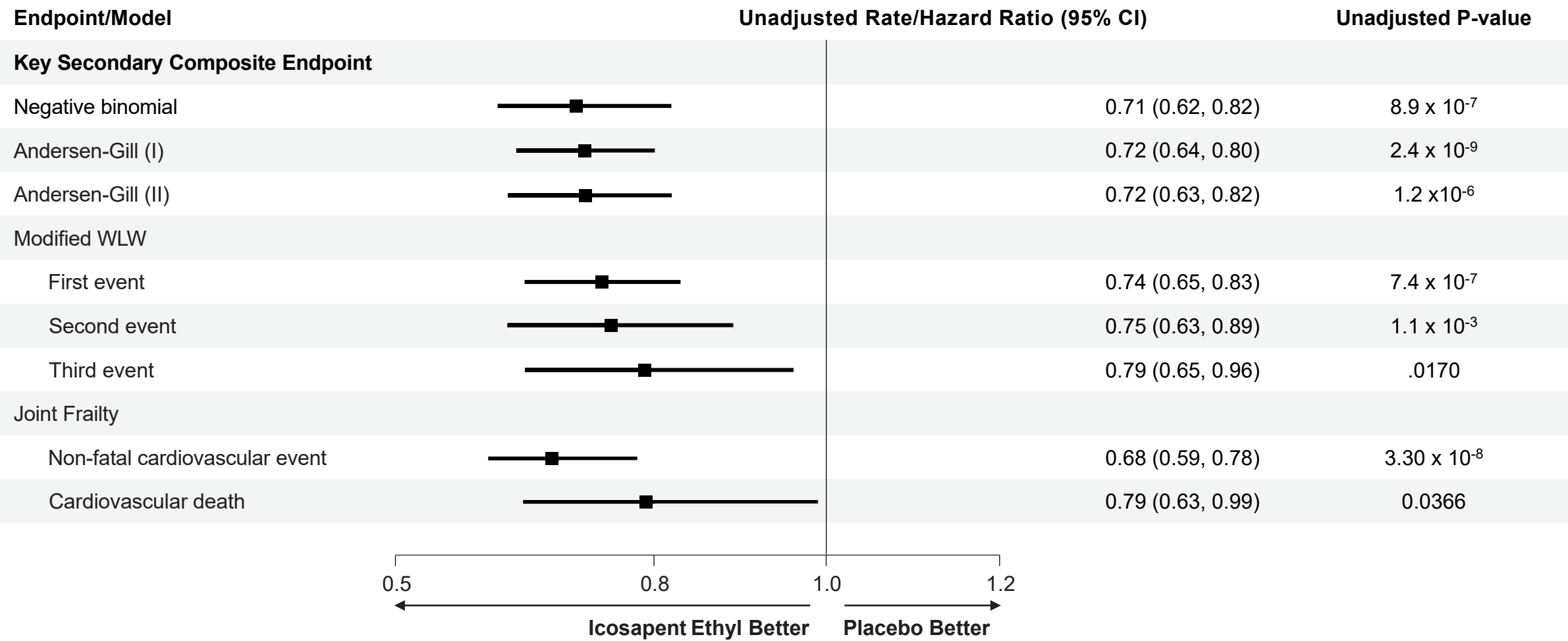
# Total Primary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Unadjusted)



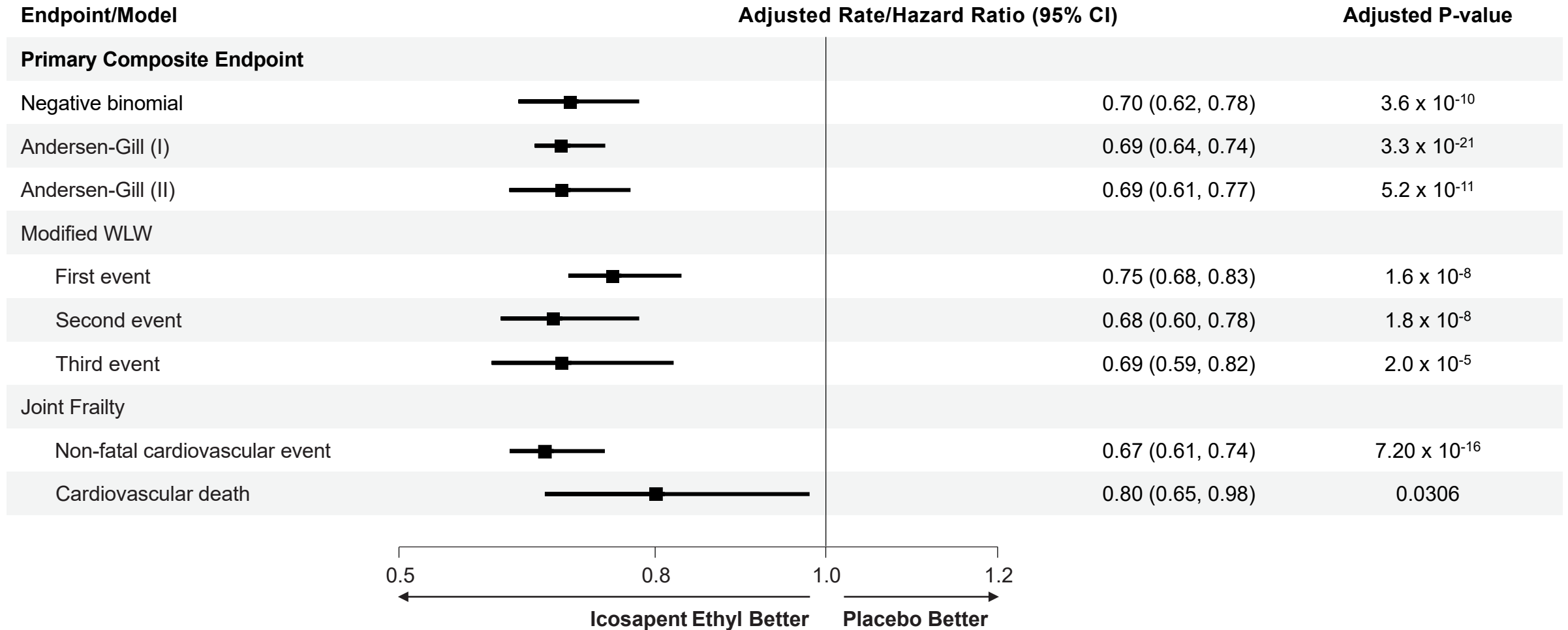


# Total Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Unadjusted)



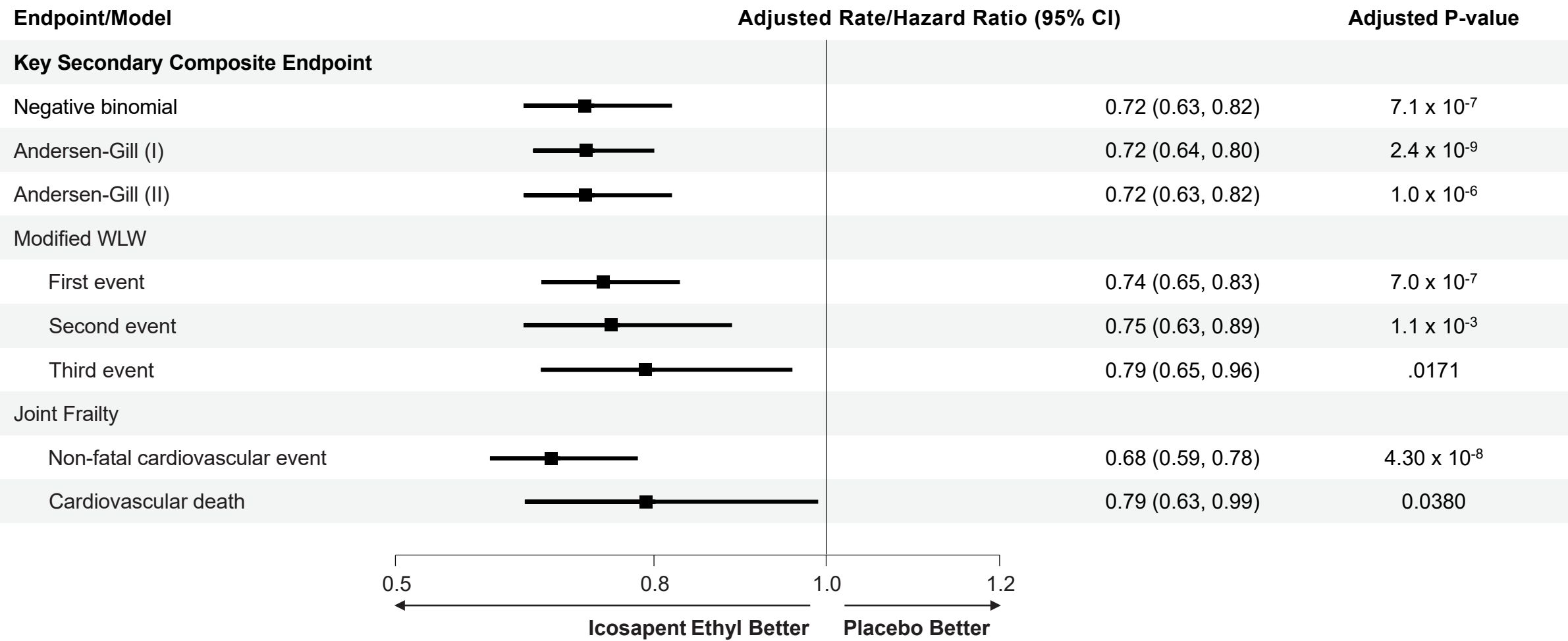


# Total Primary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Adjusted)

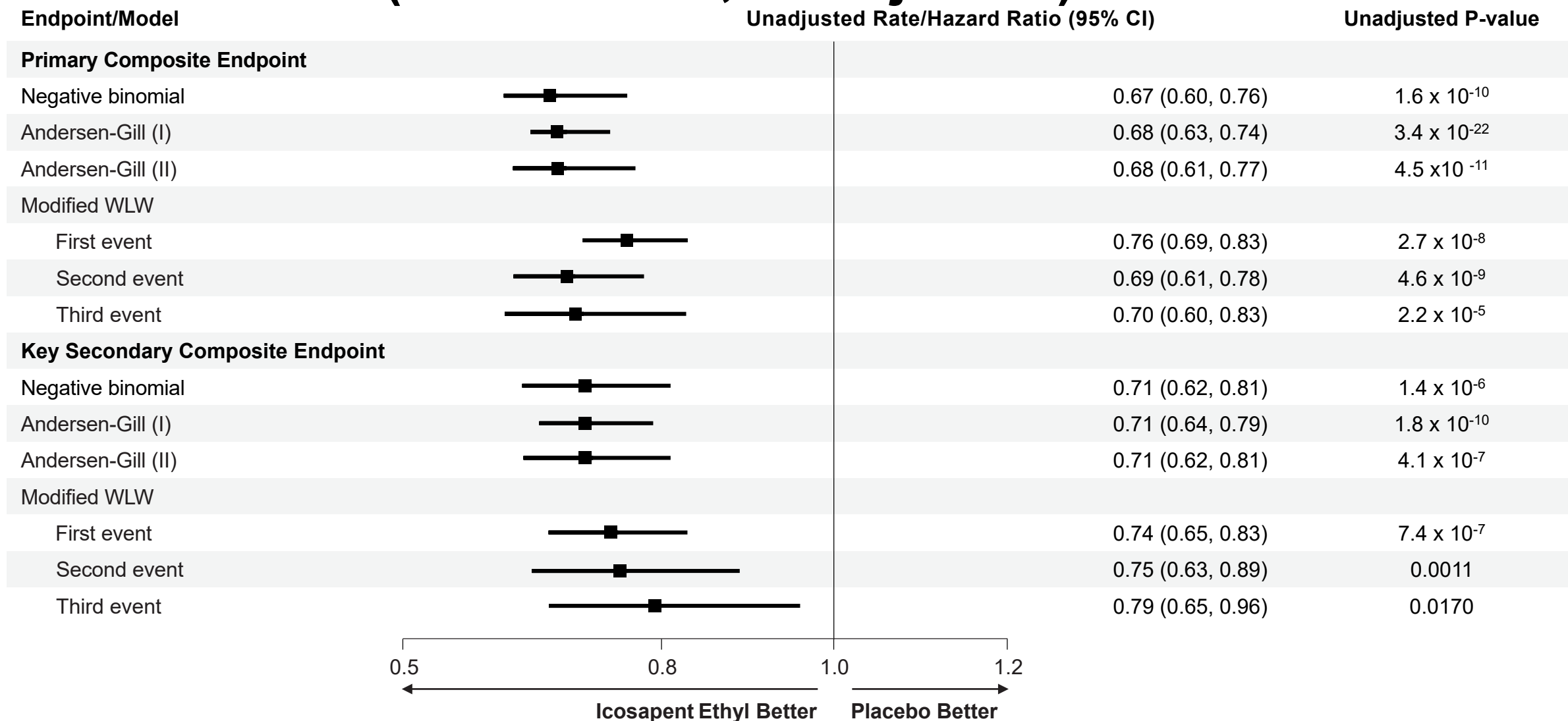


# Total Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Reduced Dataset, Adjusted)

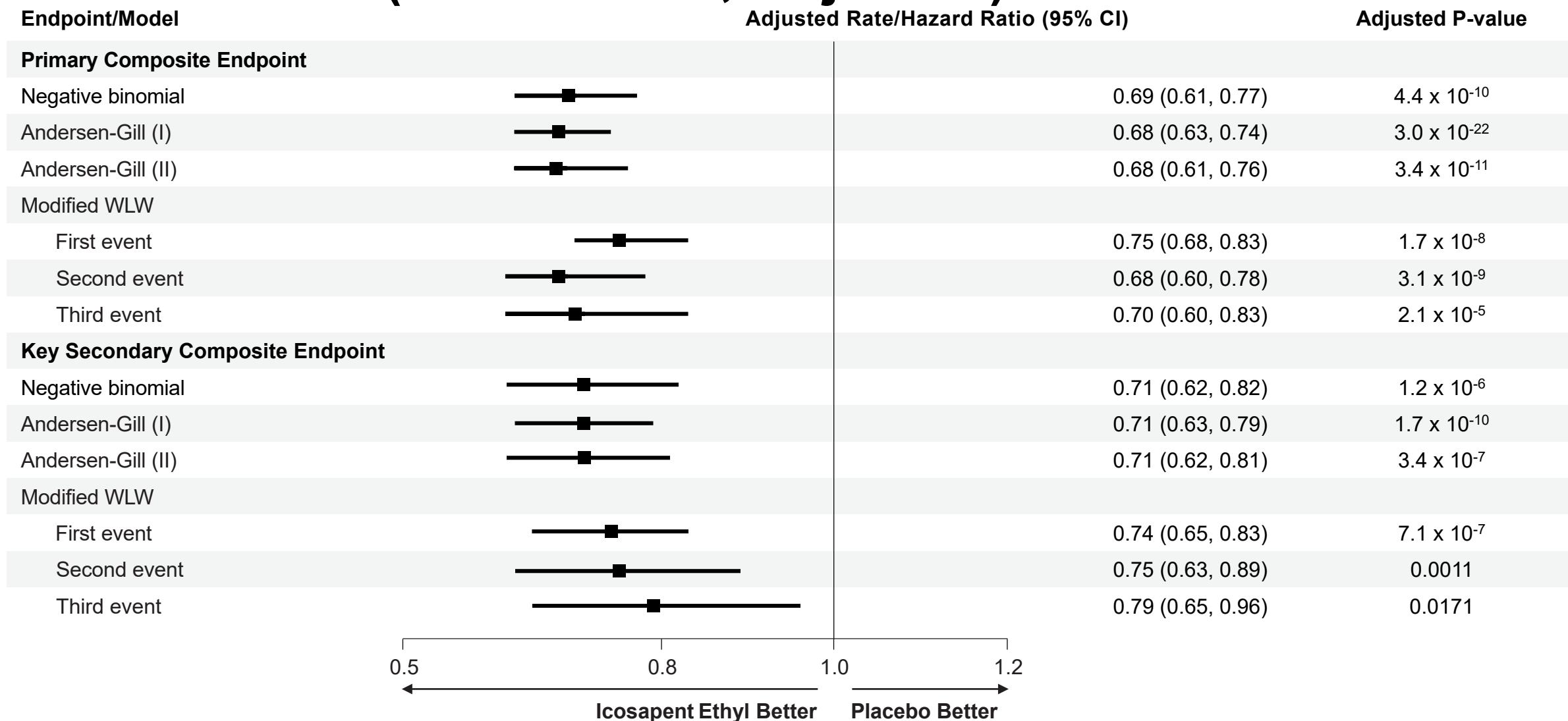




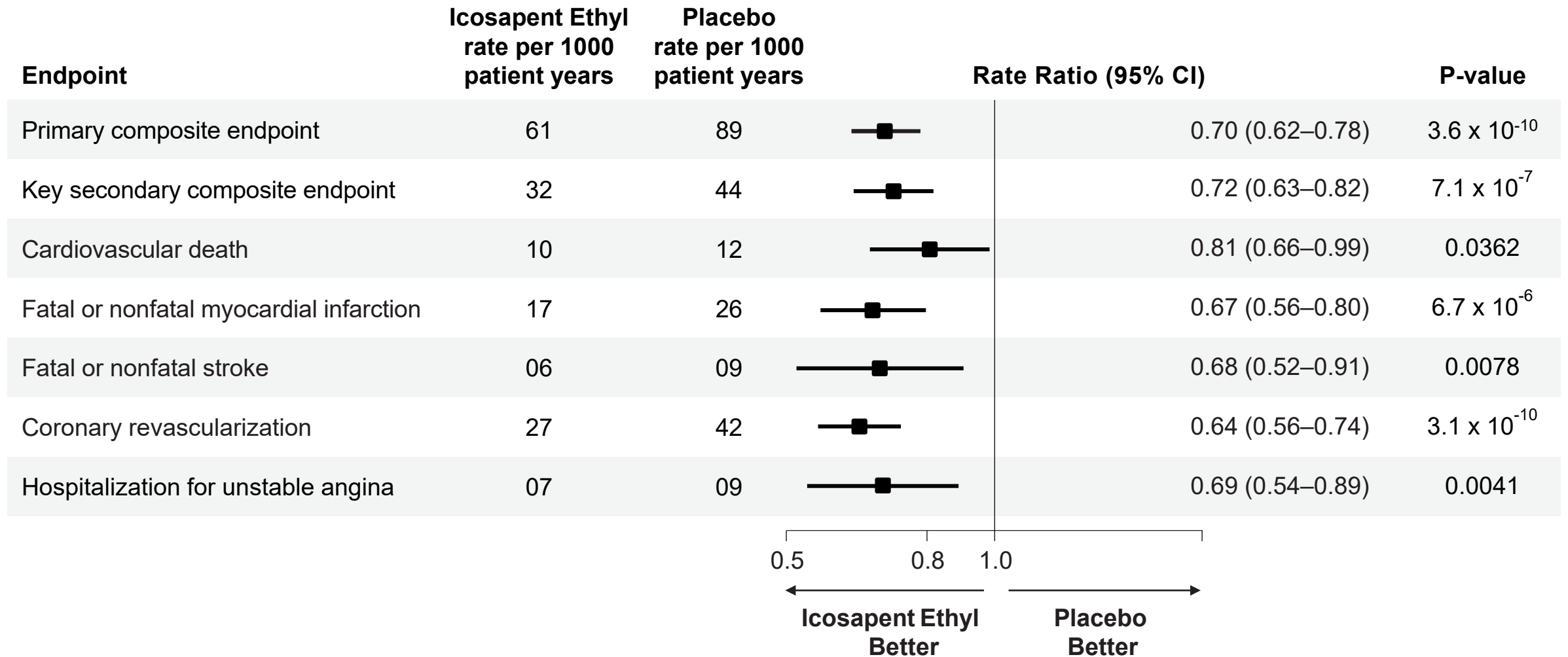
# Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences (Full Dataset, Unadjusted)



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



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



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

