

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

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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.

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REDUCE-IT Study PI and Committees



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Clinical Endpoint Committee

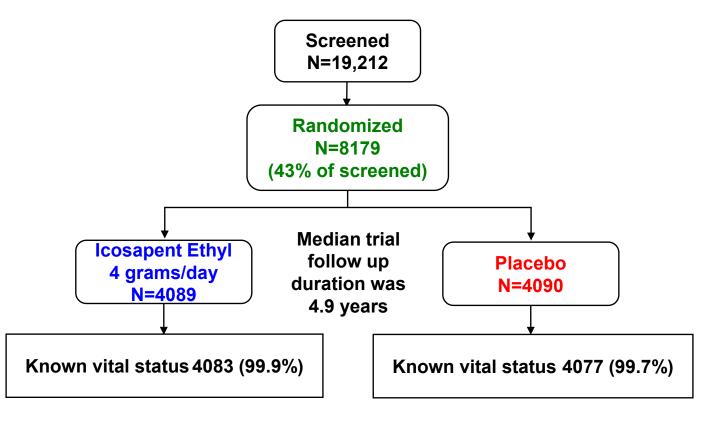
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Independent Academic Statistical Analysis

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

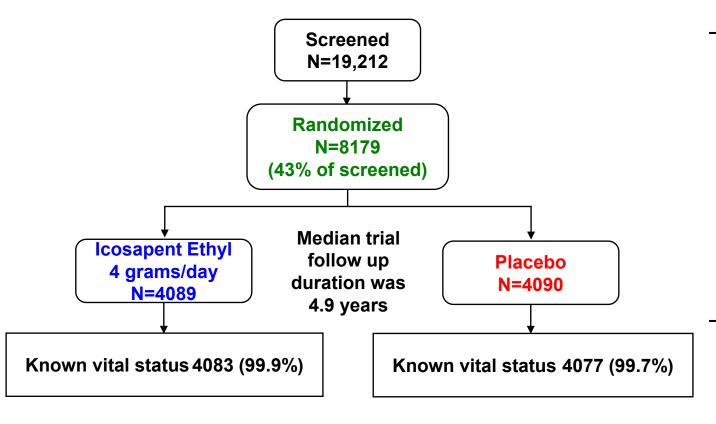
Key Secondary Endpoint Events: CV death, nonfatal MI, nonfatal stroke

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

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

REDUCE-IT Design





- 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

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

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

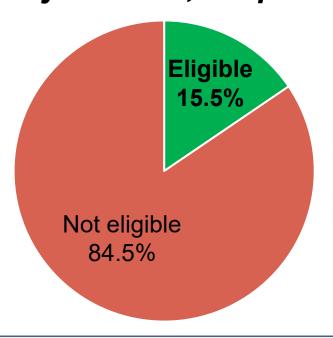
Bhatt DL, Steg PG, Miller M, et al. N Engl J Med. 2019; 380:11-22.

Generalizability of REDUCE-IT in Patients with Stable CAD An analysis of 24,146 patients from the CLARIFY registry

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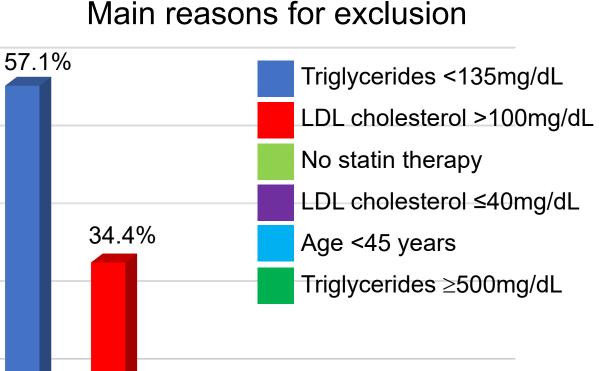
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20



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



12.6%

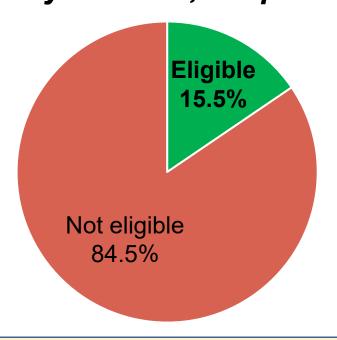
3.8%

0.6%

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

15.2%

Generalizability of REDUCE-IT in Patients with Stable CAD An analysis of 24,146 patients from the CLARIFY registry

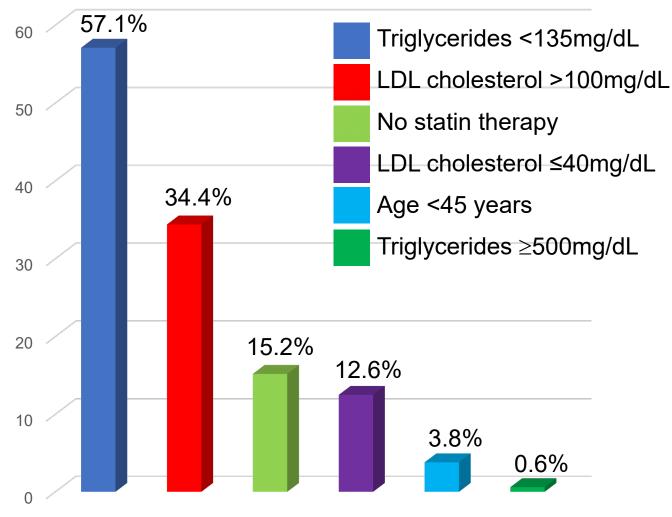


Key Inclusion Criteria for CLARIFY Analysis

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- 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

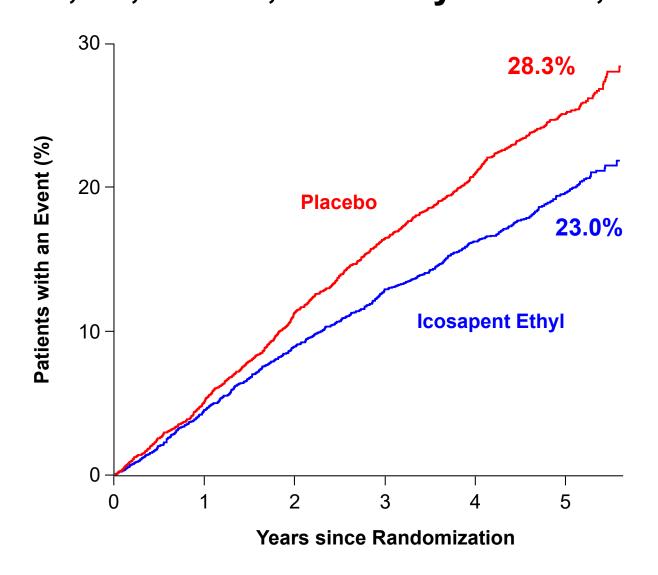
Main reasons for exclusion



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%

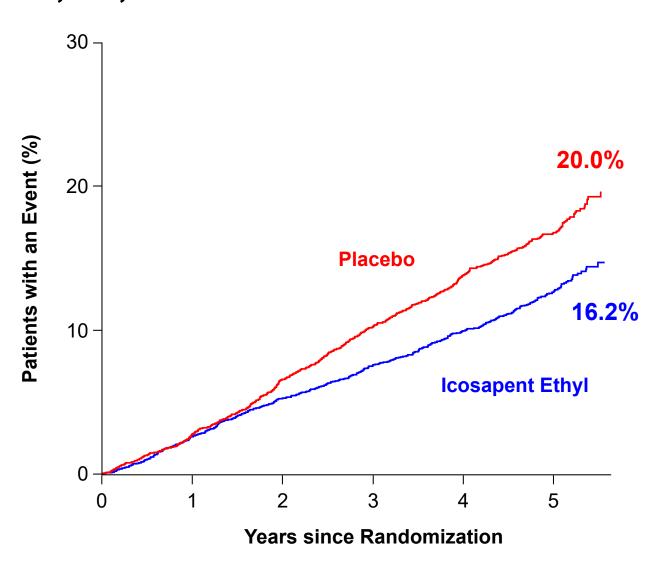
ARR = 4.8%

NNT = 21 (95% CI, 15–33)

P=0.0000001

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=0.000006

Prespecified Hierarchical Testing



Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo	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
	0.4 1.0	1.4				

Icosapent Ethyl Better

Placebo Better

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 Coduce-it



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		

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019. Bhatt DL. ACC 2019, New Orleans.

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

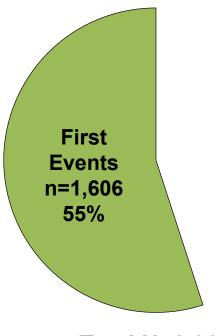
Key Medical Therapy



	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Λ :-1:-1-1-1		,
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 Creduce-it

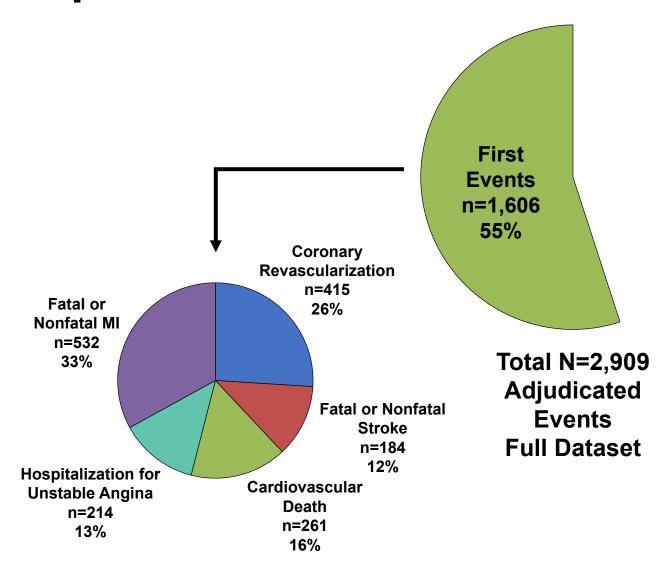




Total N=2,909 **Adjudicated Events Full Dataset**

Proportions of First and Subsequent Events



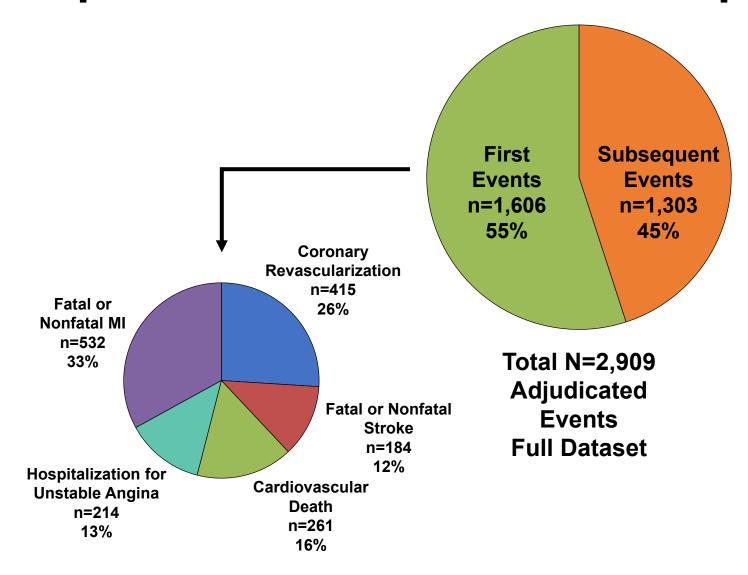


First Events

Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019.

Proportions of First and Subsequent Events



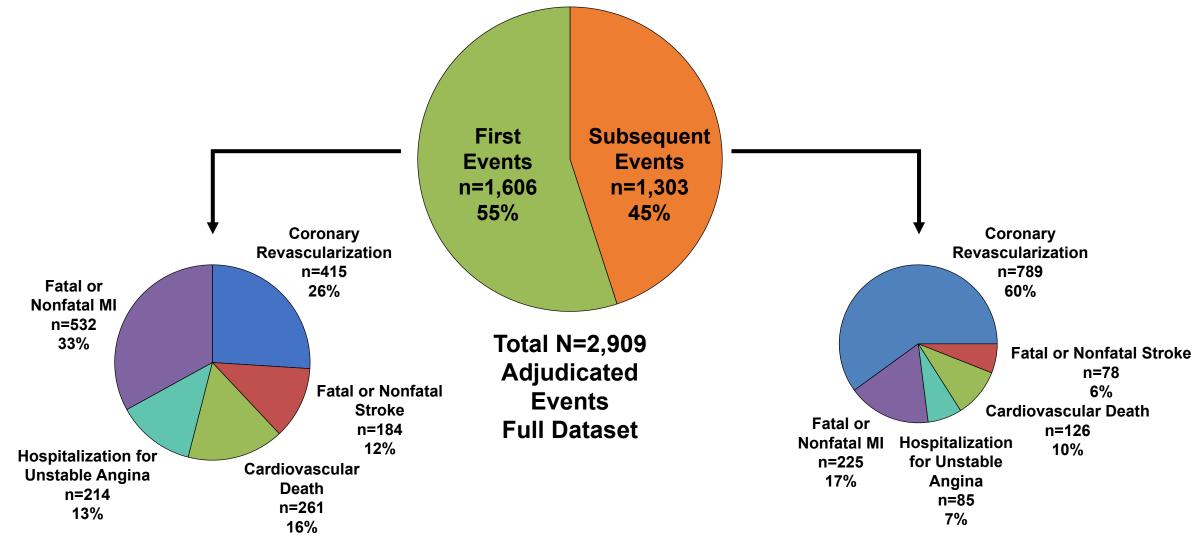


First Events

Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019.

Proportions of First and Subsequent Events





First Events

Subsequent Events

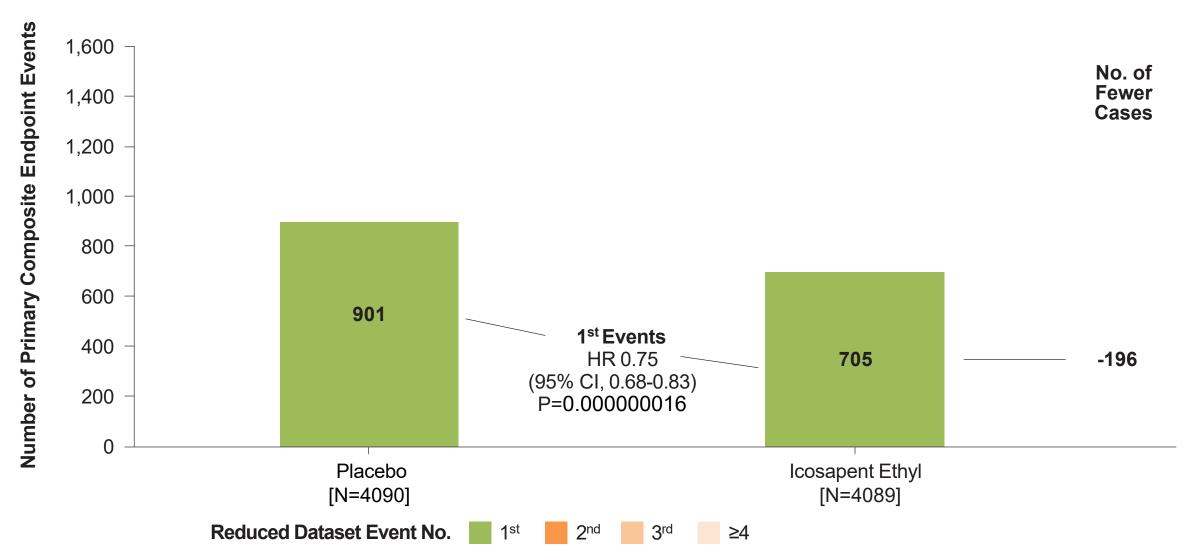
Event Counts



Events on the Same Day:

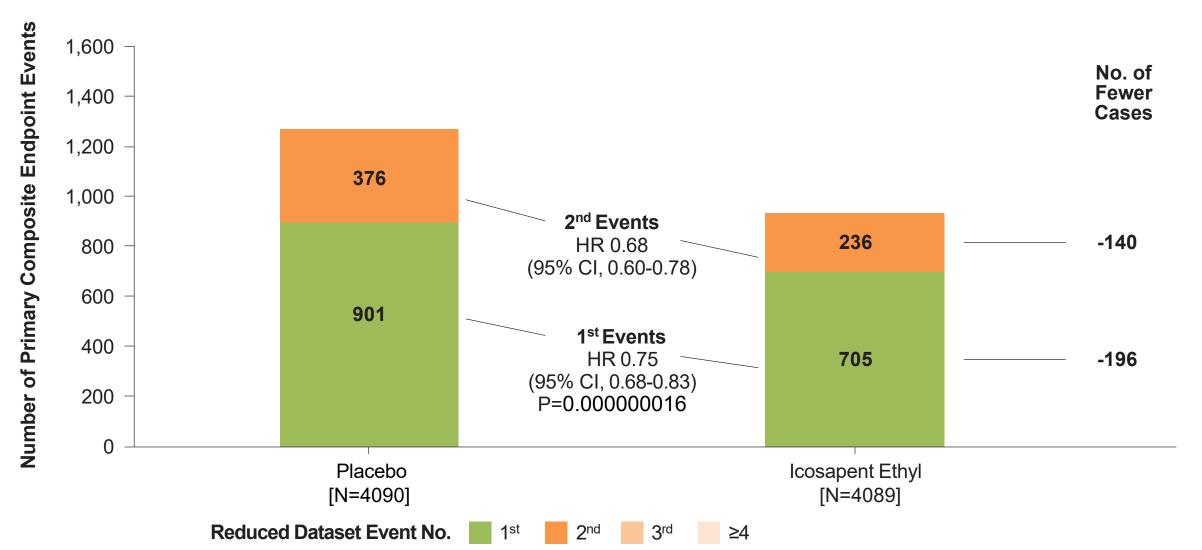
- To improve model performance an event-bundling approach was employed
 - Nonfatal events occurring on the same day as a CV death were excluded and, at most, one nonfatal event was counted on any given day
 - Analyses using this approach are identified as using the "Reduced Dataset" – a more conservative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





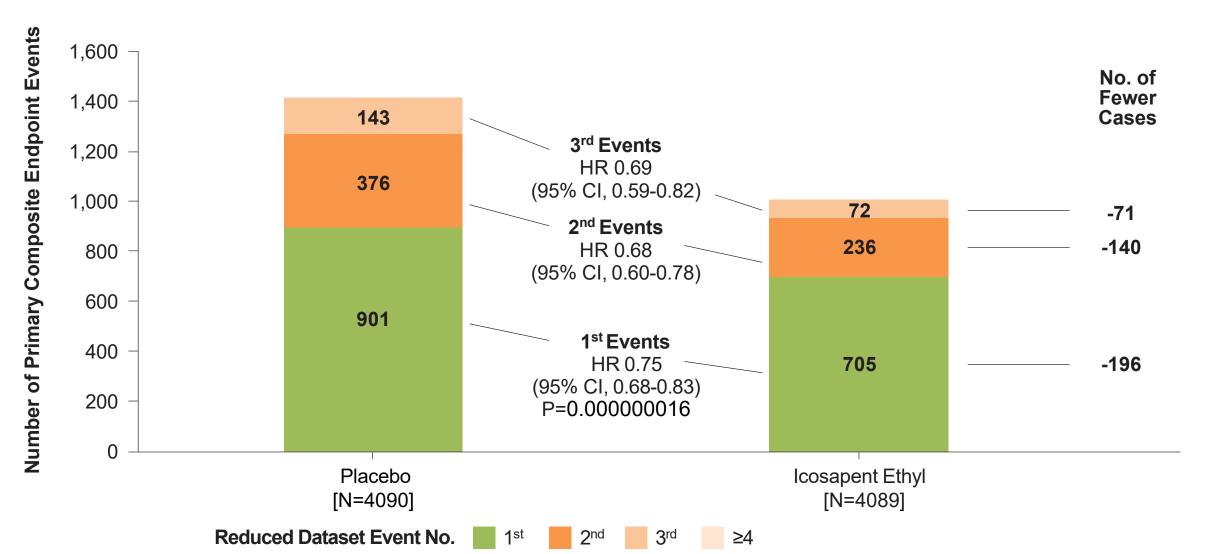
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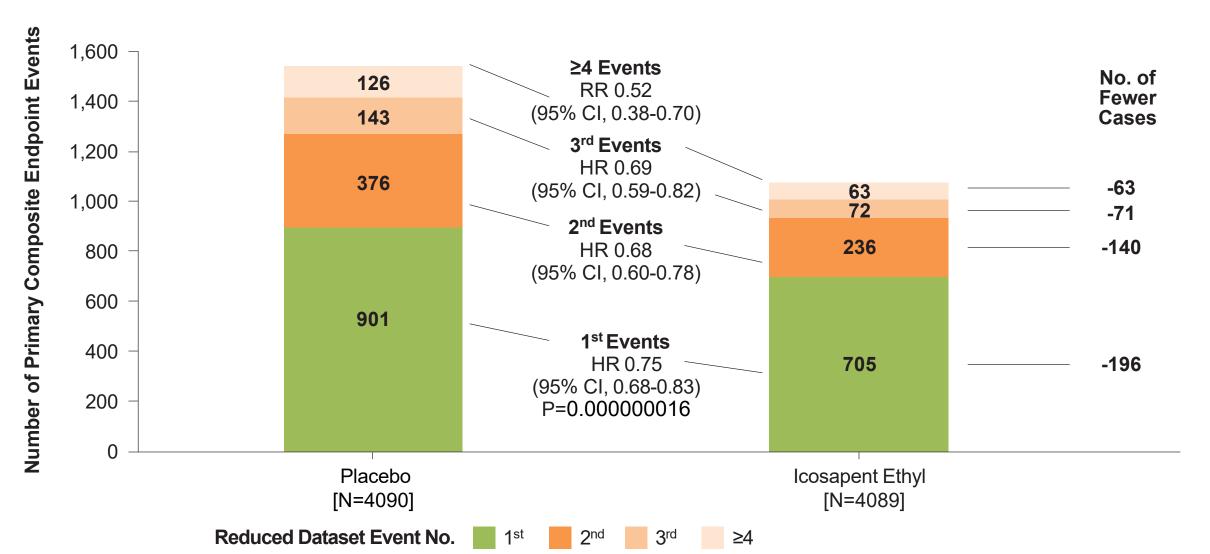
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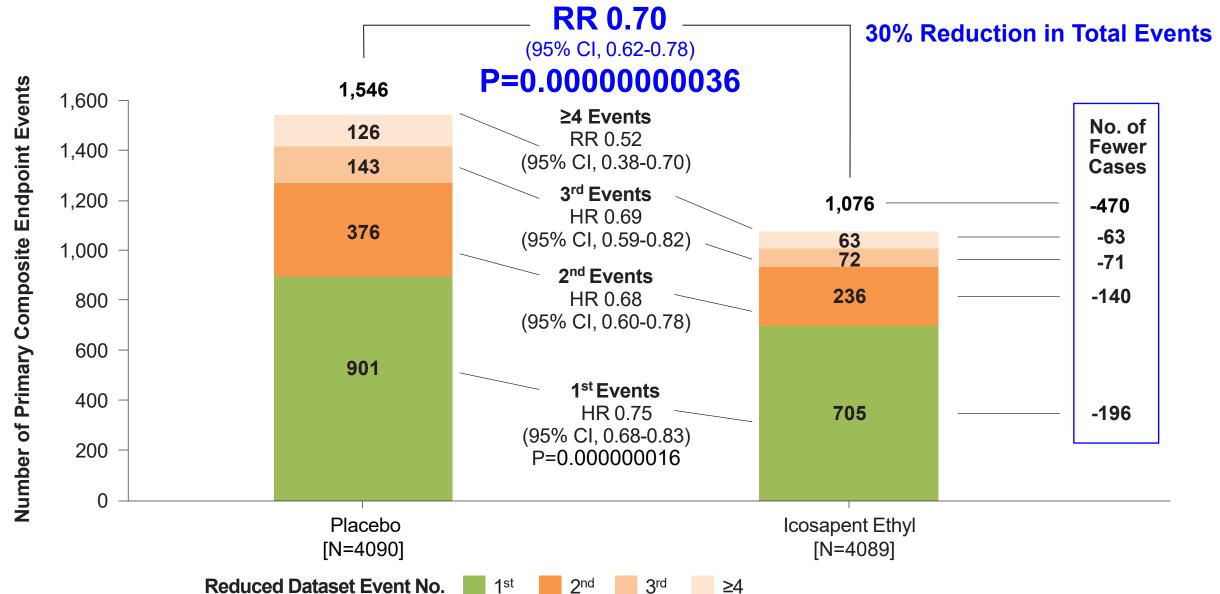
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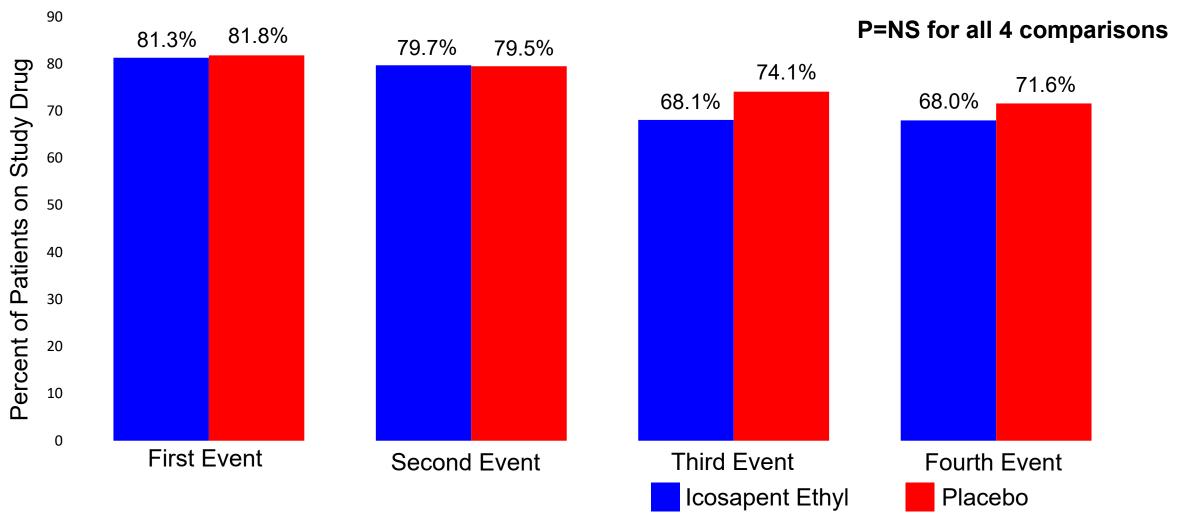




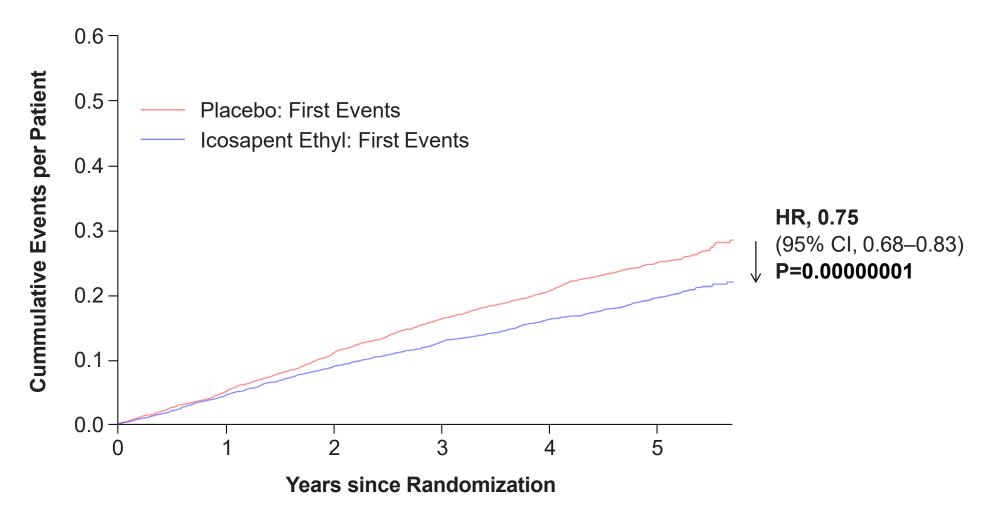
Adherence

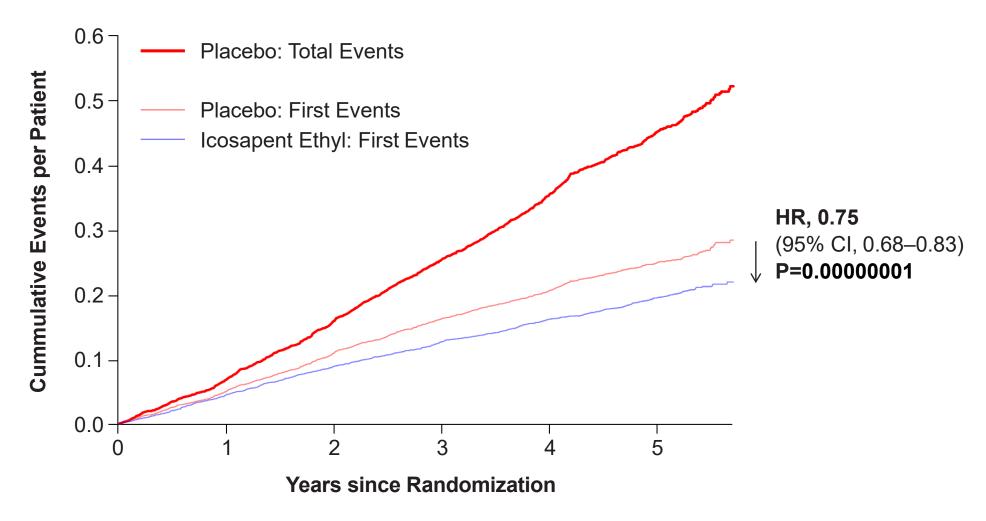


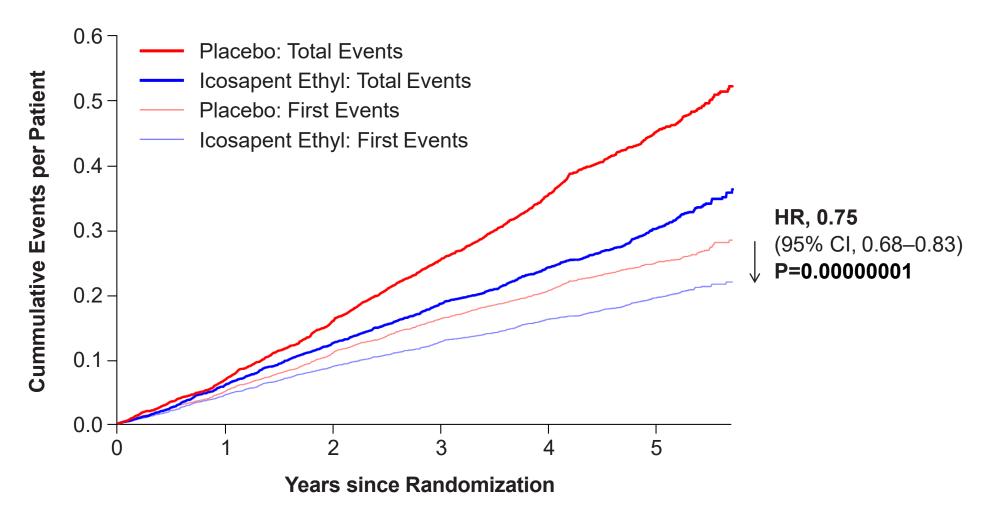
- As is common in long-term trials, study drug adherence waned over time
- Despite this, there was strong sustained treatment effect on total events

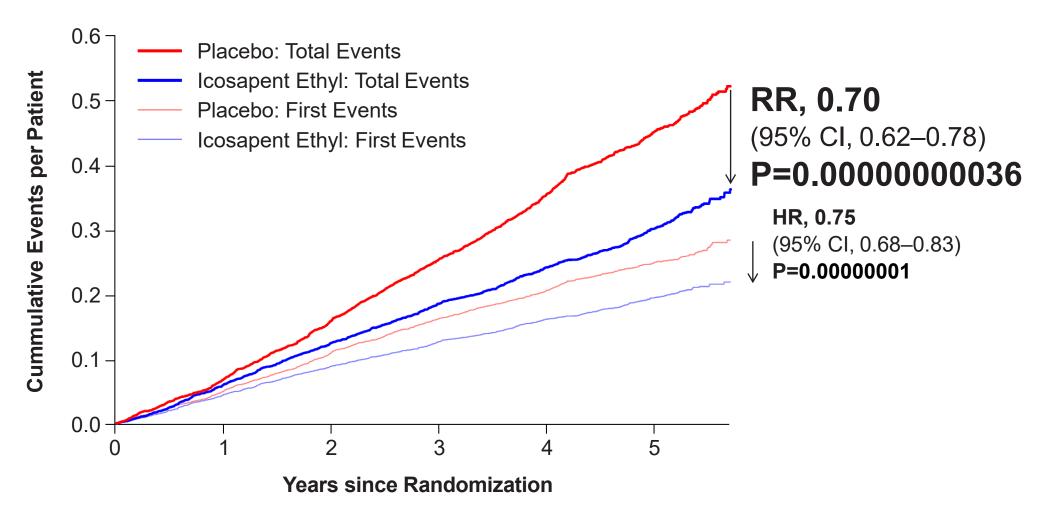


Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019. Bhatt DL. ACC 2019, New Orleans.



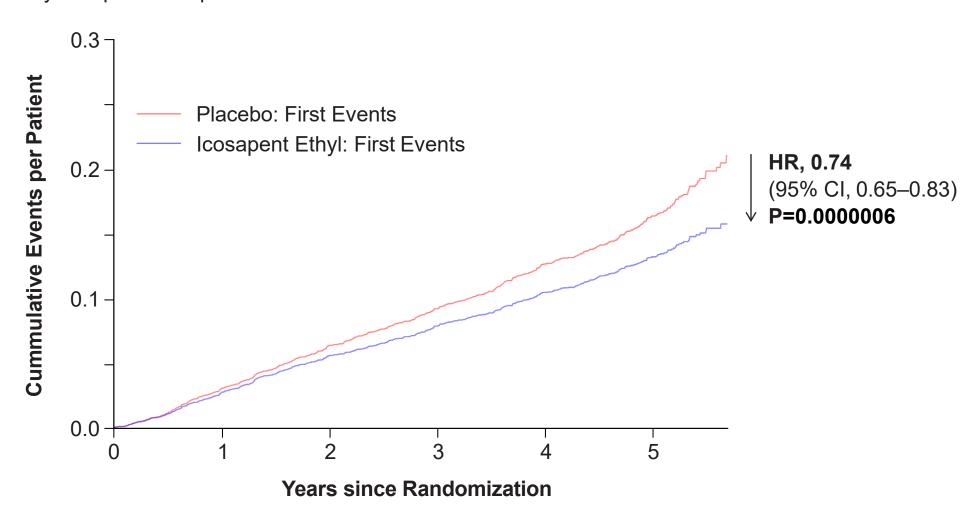






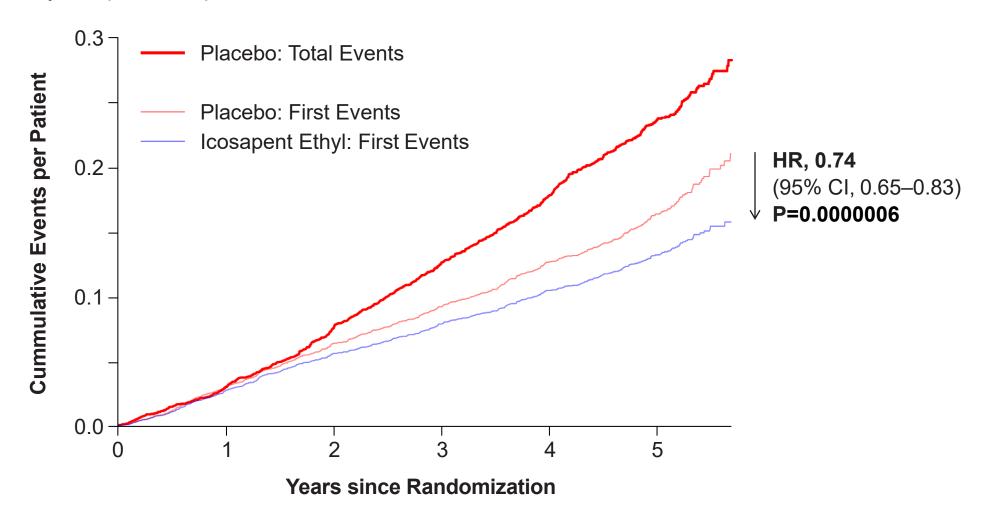
Time to First Event Key Secondary: CV Death, MI, Stroke





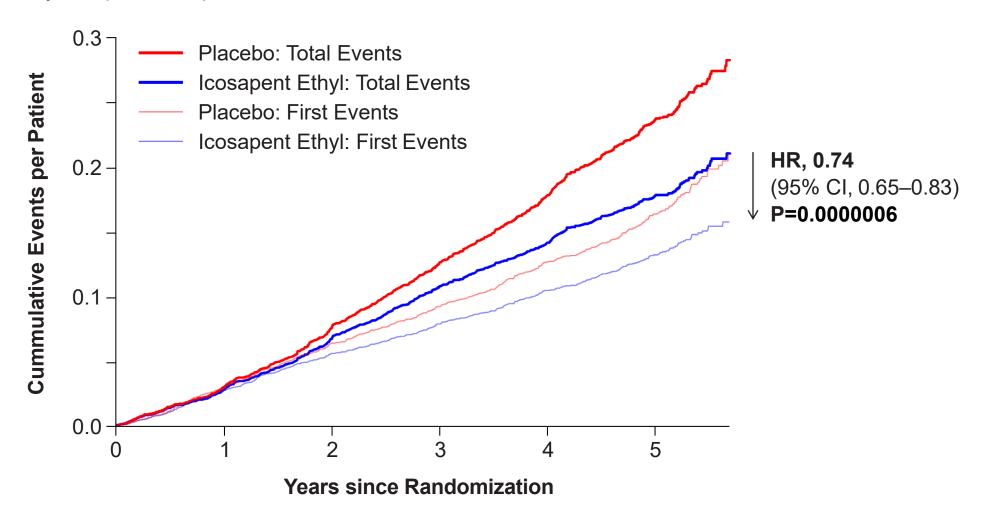
Total (First and Subsequent) Events Key Secondary: CV Death, MI, Stroke





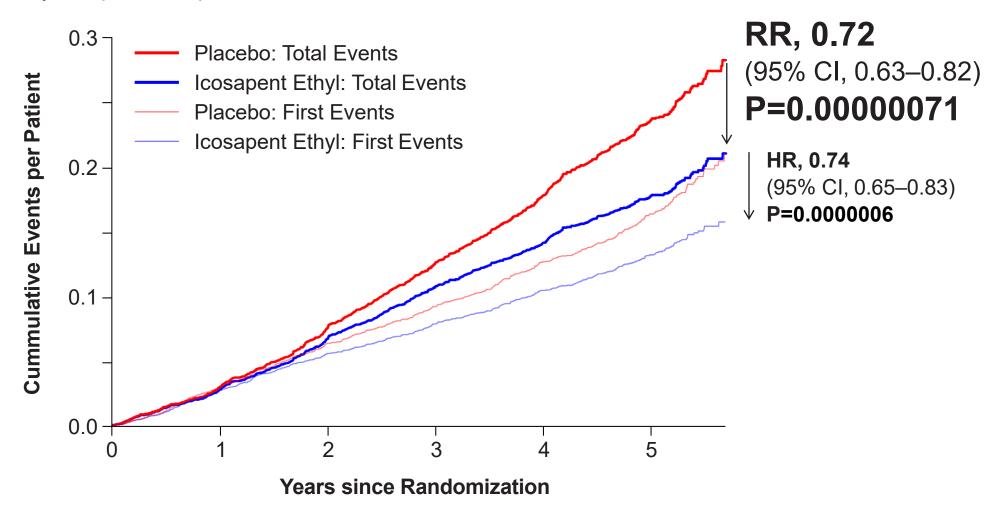
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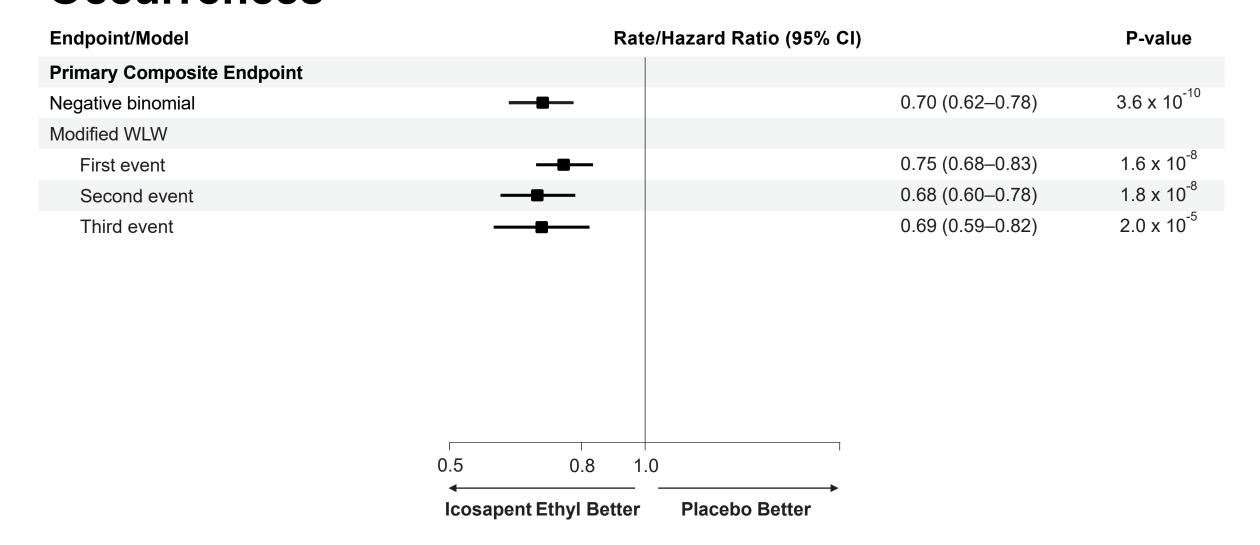
Total (First and Subsequent) Events Key Secondary: CV Death, MI, Stroke





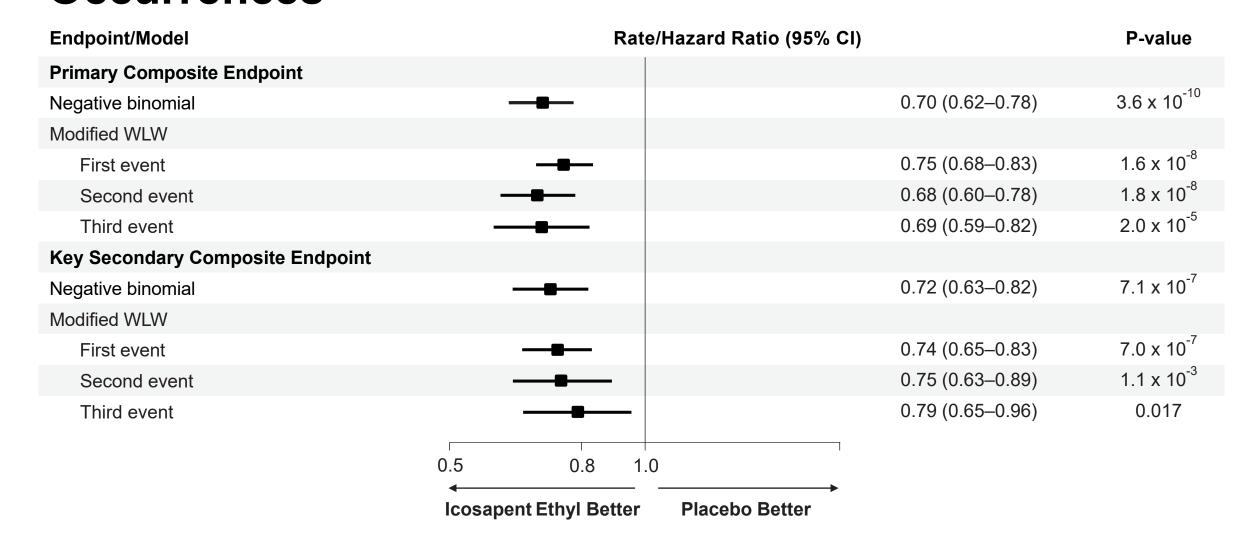
Total Primary and Key Secondary Composite Endpoint Events and First, Second, and Third Occurrences





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





Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles



TOTAL EVENTS – Primary Compos	site 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
0.2	0.6 1.0 1.4 1.8			*P (interact	ion) = 0.17
	Icosapent Ethyl Placebo Better Better				

Bhatt DL. ACC 2019, New Orleans.

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 costeffectiveness analyses now underway





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

• 25% reduction in first cardiovascular events



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



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



- 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

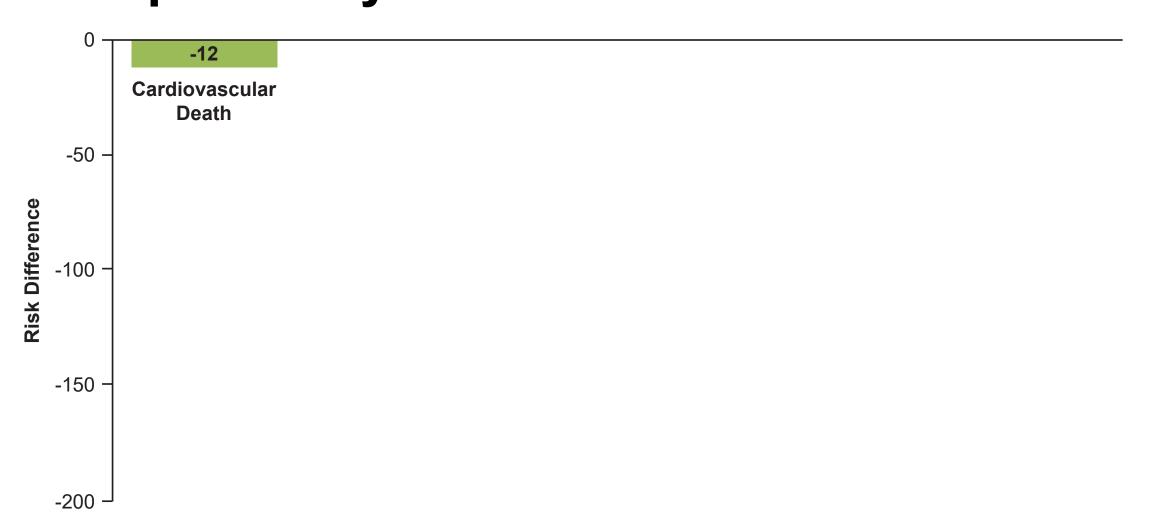


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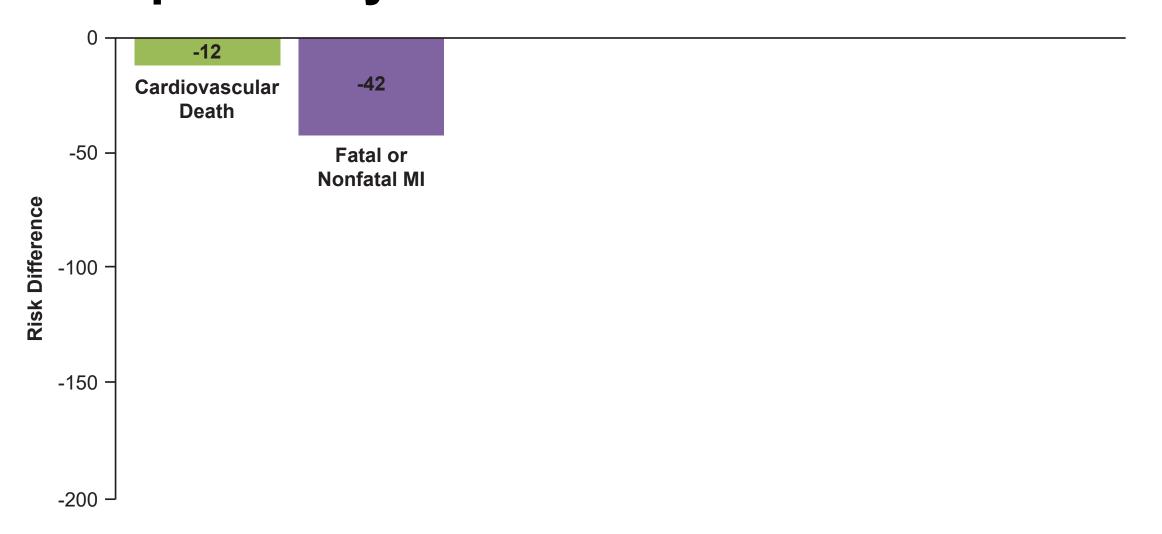
- 25% reduction in first cardiovascular events
- 32% reduction in second cardiovascular events
- 31% reduction in third cardiovascular events
- 48% reduction in fourth or more cardiovascular events

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

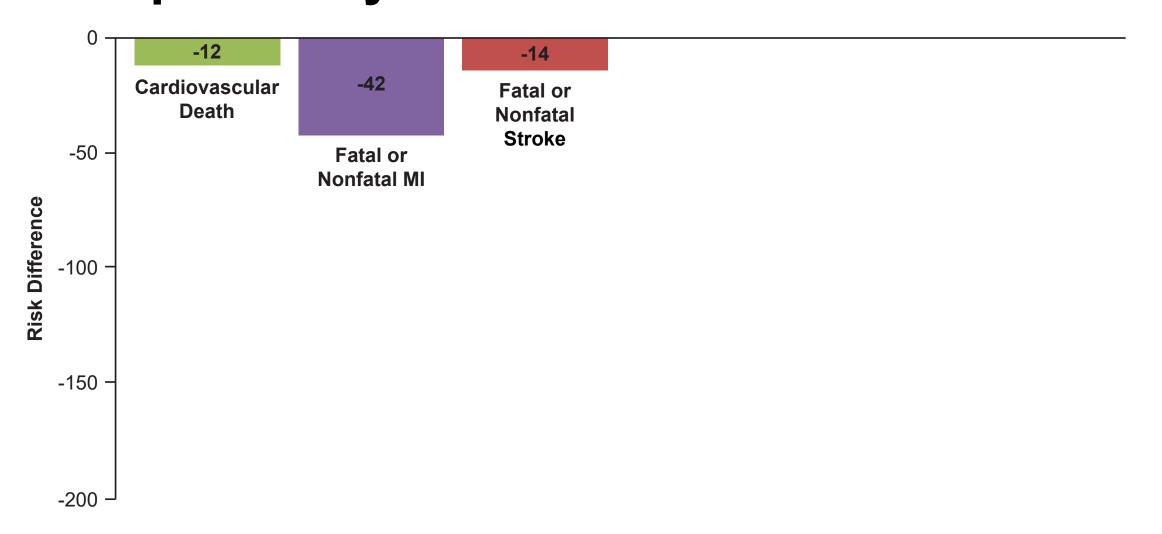




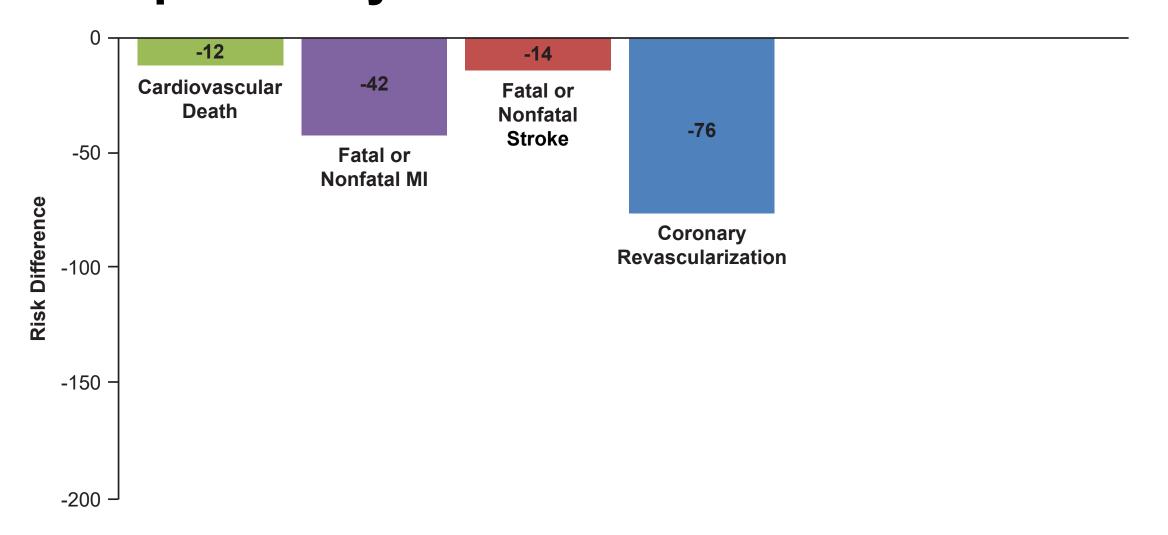




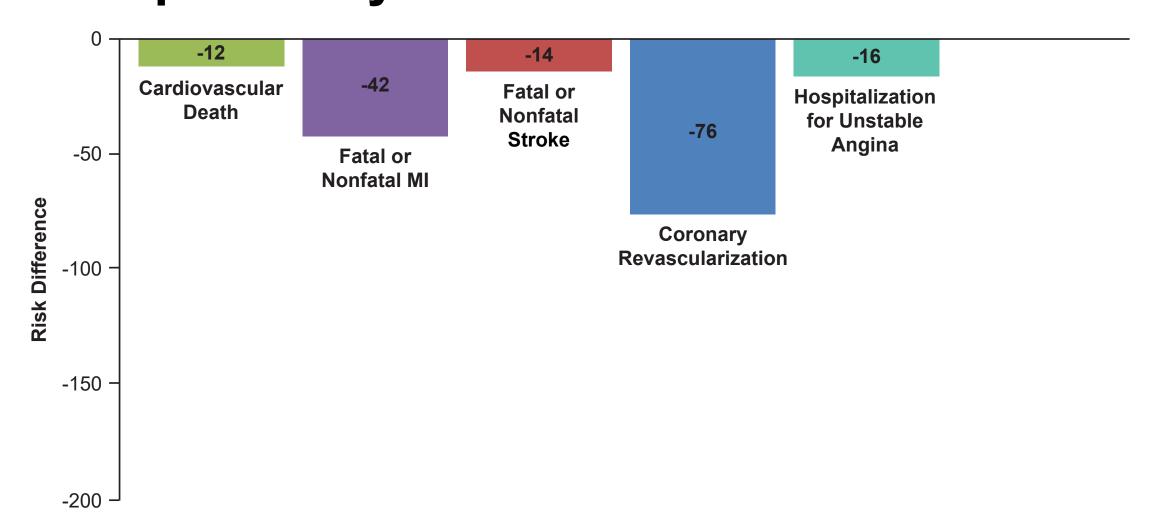




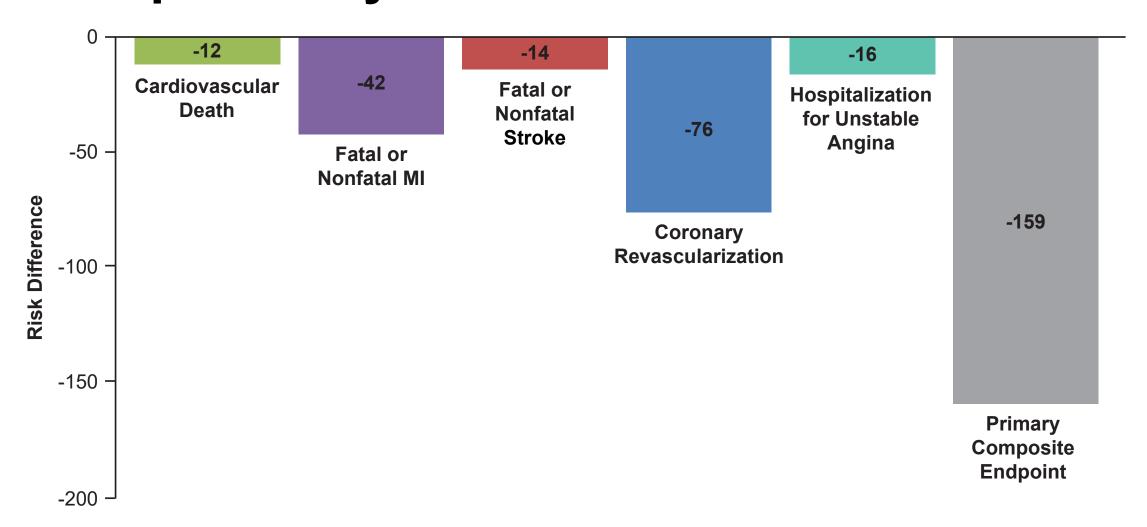












We thank the investigators, the study coordinators, (reduce-it and especially the 8,179 patients in REDUCE-IT!







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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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.

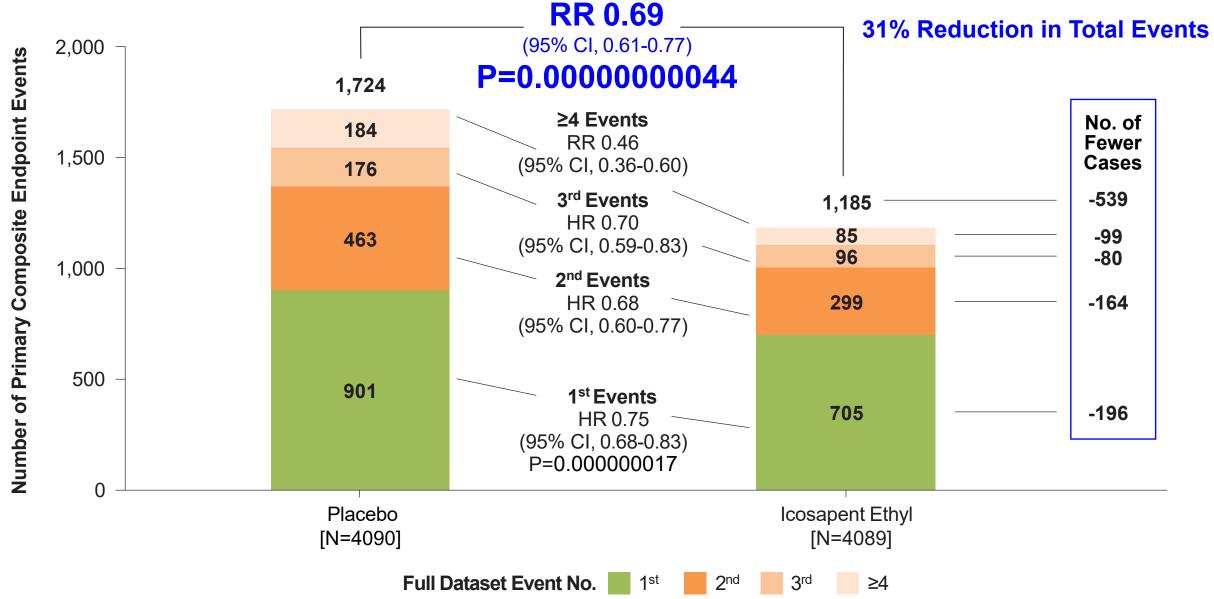
TGs were also measured from blood drawn at the randomization visit, but randomization values were not utilized for study qualification. Randomization values did not always fall within the inclusion criteria that were previously met at a qualifying visit.

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





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



Endpoint/Model	Una	djusted Rate/H	lazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint					
Negative binomial ——				0.68 (0.61, 0.77)	1.5 x 10 ⁻¹⁰
Andersen-Gill (I)	—			0.69 (0.64, 0.74)	3.5 x 10 ⁻²¹
Andersen-Gill (II)	—			0.69 (0.61, 0.77)	9.1 x 10 ⁻¹¹
Modified WLW					
First event				0.76 (0.69, 0.83)	2.7 x 10 ⁻⁸
Second event	—			0.69 (0.60, 0.79)	2.7 x 10 ⁻⁸
Third event				0.69 (0.59, 0.82)	2.1 x 10 ⁻⁵
Key Secondary Composite Endpoint					
Negative binomial	=			0.71 (0.62, 0.82)	8.9 x 10 ⁻⁷
Andersen-Gill (I)	-			0.72 (0.64, 0.80)	2.4 x 10 ⁻⁹
Andersen-Gill (II)	-			0.72 (0.63, 0.82)	1.2 x10 ⁻⁶
Modified WLW					
First event				0.74 (0.65, 0.83)	7.4 x 10 ⁻⁷
Second event				0.75 (0.63, 0.89)	1.1 x 10 ⁻³
Third event	=	-		0.79 (0.65, 0.96)	0.0170
0.5	0.8	1.0	1.2		
•	Icosapent Ethyl Bet	ter Placebo	Better		

Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019.

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



Endpoint/Model			Adjusted Rate/H	lazard Ratio (95	% CI)	Adjusted P-value
Primary Composite Endpoint						
Negative binomial	_				0.70 (0.62, 0.78)	3.6 x 10 ⁻¹⁰
Andersen-Gill (I)					0.69 (0.64, 0.74)	3.3 x 10 ⁻²¹
Andersen-Gill (II)	_	_			0.69 (0.61, 0.77)	5.2 x 10 ⁻¹¹
Modified WLW						
First event					0.75 (0.68, 0.83)	1.6 x 10 ⁻⁸
Second event	_				0.68 (0.60, 0.78)	1.8 x 10 ⁻⁸
Third event		_			0.69 (0.59, 0.82)	2.0 x 10 ⁻⁵
Key Secondary Composite Endpoin	t					
Negative binomial	-				0.72 (0.63, 0.82)	7.1 x 10 ⁻⁷
Andersen-Gill (I)					0.72 (0.64, 0.80)	2.4 x 10 ⁻⁹
Andersen-Gill (II)	-				0.72 (0.63, 0.82)	1.0 x 10 ⁻⁶
Modified WLW						
First event					0.74 (0.65, 0.83)	7.0 x 10 ⁻⁷
Second event	-		_		0.75 (0.63, 0.89)	1.1 x 10 ⁻³
Third event					0.79 (0.65, 0.96)	0.0171
	0.5	0.8	1.0	1.2		
att DL Otal DO Millar Market		Icosapent Eth	nyl Better Place	oo Better		

Bhatt DL, Steg PG, Miller M, et al. J Am Coll Cardiol. 2019.

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



Endpoint/Model			Unadjus	ted Rate/Ha	zard Ratio	(95% CI)	Unadjusted P-value
Primary Composite Endpoint							
Negative binomial						0.68 (0.61, 0.77)	1.5 x 10 ⁻¹⁰
Andersen-Gill (I)		-				0.69 (0.64, 0.74)	3.5 x 10 ⁻²¹
Andersen-Gill (II)						0.69 (0.61, 0.77)	9.1 x 10 ⁻¹¹
Modified WLW							
First event						0.76 (0.69, 0.83)	2.7 x 10 ⁻⁸
Second event	-					0.69 (0.60, 0.79)	2.7 x 10 ⁻⁸
Third event	_	_				0.69 (0.59, 0.82)	2.1 x 10 ⁻⁵
Joint Frailty							
Non-fatal cardiovascular event	-					0.66 (0.60, 0.73)	7.40 x 10 ⁻¹⁷
Cardiovascular death						0.80 (0.65, 0.98)	0.0282
	0.5	0.8	1	.0	1.2		
	•	Icosapent E	thyl Better	Placebo B	etter		

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



Endpoint/Model	U	Inadjusted Rate/Haz	ard Ratio (95% CI)	Unadjusted P-value
Key Secondary Composite Endpoint				
Negative binomial			0.71 (0.62, 0.82)	8.9 x 10 ⁻⁷
Andersen-Gill (I)			0.72 (0.64, 0.80)	2.4 x 10 ⁻⁹
Andersen-Gill (II)			0.72 (0.63, 0.82)	1.2 x10 ⁻⁶
Modified WLW				
First event			0.74 (0.65, 0.83)	7.4 x 10 ⁻⁷
Second event			0.75 (0.63, 0.89)	1.1 x 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 x 10 ⁻⁸
Cardiovascular death			0.79 (0.63, 0.99)	0.0366
0.5	0.8	1.0	1.2	
•	Icosapent Ethyl	Better Placebo Bet	tter	

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 x 10 ⁻¹⁰
Andersen-Gill (I)		0.69 (0.64, 0.74)	3.3 x 10 ⁻²¹
Andersen-Gill (II)		0.69 (0.61, 0.77)	5.2 x 10 ⁻¹¹
Modified WLW			
First event		0.75 (0.68, 0.83)	1.6 x 10 ⁻⁸
Second event		0.68 (0.60, 0.78)	1.8 x 10 ⁻⁸
Third event		0.69 (0.59, 0.82)	2.0 x 10 ⁻⁵
Joint Frailty			
Non-fatal cardiovascular event		0.67 (0.61, 0.74)	7.20 x 10 ⁻¹⁶
Cardiovascular death		0.80 (0.65, 0.98)	0.0306
	0.5 0.8	1.0 1.2	
	Icosapent Et	hyl Better Placebo Better	

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



Endpoint/Model		Adjusted Rate/Haz	zard Ratio (95%	CI)	Adjusted P-value
Key Secondary Composite Endpoint					
Negative binomial				0.72 (0.63, 0.82)	7.1 x 10 ⁻⁷
Andersen-Gill (I)				0.72 (0.64, 0.80)	2.4 x 10 ⁻⁹
Andersen-Gill (II)				0.72 (0.63, 0.82)	1.0 x 10 ⁻⁶
Modified WLW					
First event				0.74 (0.65, 0.83)	7.0 x 10 ⁻⁷
Second event				0.75 (0.63, 0.89)	1.1 x 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 x 10 ⁻⁸
Cardiovascular death				0.79 (0.63, 0.99)	0.0380
0.5	0.8	1.0	1.2		
•	Icosapent Ethy	l Better Placebo	Better		

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



Ratio (95% CI)	Unadjusted P-value	
0.67 (0.60, 0.76)	1.6 x 10 ⁻¹⁰	
0.68 (0.63, 0.74)	3.4 x 10 ⁻²²	
0.68 (0.61, 0.77)	4.5 x10 ⁻¹¹	
0.76 (0.69, 0.83)	2.7 x 10 ⁻⁸	
0.69 (0.61, 0.78)	4.6 x 10 ⁻⁹	
0.70 (0.60, 0.83)	2.2 x 10 ⁻⁵	
0.71 (0.62, 0.81)	1.4 x 10 ⁻⁶	
0.71 (0.64, 0.79)	1.8 x 10 ⁻¹⁰	
0.71 (0.62, 0.81)	4.1 x 10 ⁻⁷	
0.74 (0.65, 0.83)	7.4 x 10 ⁻⁷	
0.75 (0.63, 0.89)	0.0011	
0.79 (0.65, 0.96)	0.0170	
2		
2		

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



Adjusted P-value
.61, 0.77) 4.4 x 10 ⁻¹⁰
.63, 0.74) 3.0 x 10 ⁻²²
.61, 0.76) 3.4 x 10 ⁻¹¹
.68, 0.83) 1.7 x 10 ⁻⁸
.60, 0.78) 3.1 x 10 ⁻⁹
.60, 0.83) 2.1 x 10 ⁻⁵
.62, 0.82) 1.2 x 10 ⁻⁶
.63, 0.79) 1.7 x 10 ⁻¹⁰
.62, 0.81) 3.4 x 10 ⁻⁷
.65, 0.83) 7.1 x 10 ⁻⁷
.63, 0.89) 0.0011
.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	Ra	te Ratio (95% CI)	P-value
Primary composite endpoint	61	89		0.70 (0.62–0.78)	3.6 x 10 ⁻¹⁰
Key secondary composite endpoint	32	44		0.72 (0.63–0.82)	7.1 x 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 x 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 x 10 ⁻¹⁰
Hospitalization for unstable angina	07	09		0.69 (0.54–0.89)	0.0041
		0.5	0.8 1.0) Placebo	
		11	Better	Better	

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

TIME TO FIRST EVENT – Primary C	omposite 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
0.2	0.6 1.0 1.4 1.8 cosapent Ethyl Placebo Better Better			*P (interact	ion) = 0.33