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Transforming the Unprecedented REDUCE-IT™ Study Results into Clinical Practice

Investor Presentation at ACC

March 18, 2019

NASDAQ: **AMRN**

Pure EPA

Vascepa®

(icosapent ethyl)

Forward-Looking Statements and Disclaimer

Forward-looking statements

- This presentation contains forward-looking statements, such as those relating to the commercial potential of Vascepa®, clinical and regulatory efforts and timelines, potential FDA approvals, intellectual property, cash flow, and other statements that are predictive in nature and that depend upon or refer to future events or conditions, including financial guidance and milestones. These statements involve known and unknown risks, uncertainties and other factors that can cause actual results to differ materially. Investors should not place undue reliance on primary data or forward-looking statements, which speak only as of the presentation date of this presentation. Please refer to the "Risk Factors" section in Amarin's most recent Form 10-K filed with the SEC and cautionary statements outlined in recent press releases for more complete descriptions of risks in an investment in Amarin.

Presentation is for investors (not drug promotion)

- This presentation is intended for communication with investors only.
- Nothing in this presentation should be construed as promoting the use of Amarin's product or product candidates.

Important Cautionary Information About These Data

Recurrent event analyses for the total primary endpoint events and for the total key secondary endpoint events in REDUCE-IT as published in the Journal of the American College of Cardiology[1] were conducted using a series of statistical models. These analyses were tertiary or exploratory endpoints; most of the models used were prespecified and one was post hoc. Each recurrent event statistical model has inherent strengths and weaknesses, with no single model considered definitive or outperforming the other models, and this is an evolving field of science. Nonetheless, results from the total primary and total key secondary endpoint events analyses are consistent across the various recurrent event statistical models and are also consistent with the original primary and secondary endpoint results. Together, the REDUCE-IT recurrent event analyses and the original primary and key secondary endpoint analyses support the robustness of the clinical benefit of Vascepa therapy in reducing cardiovascular risk.

Further REDUCE-IT data assessment and data release could yield additional useful information to inform greater understanding of the trial outcome. Further detailed data assessment by Amarin and regulatory authorities will continue and take several months to complete and record. The final evaluation of the totality of the efficacy and safety data from REDUCE-IT may include some or all of the following, as well as other considerations: new information affecting the degree of treatment benefit on studied endpoints; study conduct and data robustness, quality, integrity and consistency; additional safety data considerations and risk/benefit considerations; consideration of REDUCE-IT results in the context of other clinical studies.

[1] Bhatt DL, Steg PG, Miller M, et al. Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT. J Am Coll Cardiol 2019. epub ahead of print. http://www.onlinejacc.org/content/early/2019/03/01/j.jacc.2019.02.032

Agenda

Elevated Triglycerides as a Marker of Risk

- TG levels and CV risk from population cohorts
  - Dr. Ann Marie Navar
- VA data analysis on incremental CV risk
  - Dr. William Boden

Total Event Analyses from REDUCE-IT™

- Large reduction in total ischemic events in REDUCE-IT™
  - Dr. Deepak Bhatt

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Triglycerides as a Risk Factor for Coronary Heart Disease: What measure and what cutoff?

Dr. Ann Marie Navar
Duke Clinical Research Institute
Duke University School of Medicine

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Disclosures

Dr. Ann Marie Navar discloses the following relationships – Research Grant: Significant; Amarin, Janssen, Amgen, Sanofi, and Regeneron Pharmaceuticals. Consultant/Advisory Board: Significant; Amarin, Amgen, Novonordisk, AstraZeneca, Sanofi and Regeneron; also funded by NIH K01HL133416-01.

Triglycerides are Marker of Cardiovascular Risk; How is that Marker Best Used?

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Background

- Elevated triglycerides (TGs) increase cardiovascular disease (CVD) risk
- Current hypertriglyceridemia (HTG) categorization relies on single TG measurements
- It is unclear what TG levels best correlate with CVD risk, or how those levels should be assessed

Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

Using Pooled Patient Data to Answer the Questions

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Methods and Outcome Measure

- Data from 8068 primary prevention patients in 2 large databases
  - Atherosclerosis Risk in Communities Study (ARIC)
  - Framingham Offspring Study
- Baseline characteristics:
  - 40-65 years old
  - No CVD
  - 2 or more TG measurements on record
- Outcome: time to myocardial infarction, stroke, or CV death
- Follow-up: for up to 10 years to first event

Objectives

- Determine which measure of TGs is most correlated with coronary heart disease (CHD) risk:
  - Average TG
  - Maximum TG
  - Most recent TG
  - Area under the curve of TG (triglycerides x years of exposure)
- Identify thresholds of risk
- Evaluate the association between TGs and CHD

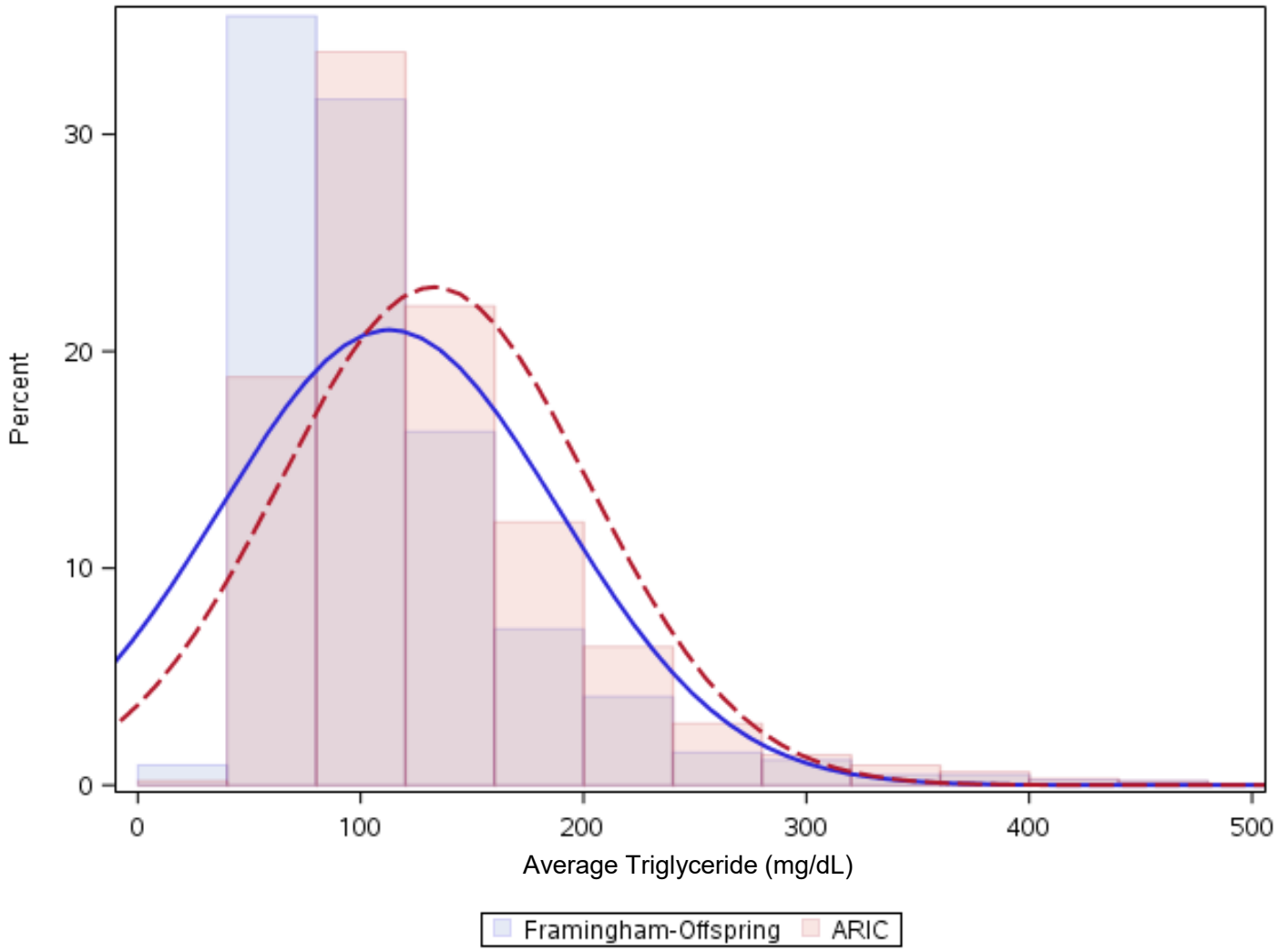
Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

Baseline Characteristics

Characteristic	Total (n=8068)	Framingham Offspring (n=2056)	ARIC (n=6012)
Age	58, 55-62	54, 50-60	59, 56-62
Female	4556 (56.5%)	1111 (54.0%)	3445 (57.3%)
White	6790 (84.2%)	2056 (100.0%)	4734 (78.7%)
Smoking	1308 (16.3%)	336 (16.3%)	972 (16.2%)
Diabetes	970 (12.1%)	123 (6.0%)	847 (14.1%)
Systolic BP	122, 112-135	123, 112-135	122, 112-135
Diastolic BP	73, 66-79	76, 70-82	72, 65-78
BMI	28, 25-31	28, 25-31	28, 25-32
Hypertension Treatment	2170 (27.0%)	393 (19.1%)	1777 (29.7%)
Statin	629 (7.8%)	120 (5.8%)	509 (8.5%)
Total Cholesterol	200, 178-225	204, 181-230	199, 177-224
HDL Cholesterol	48, 39-61	50, 40-61	47, 39-60
LDL Cholesterol	122, 101-145	125, 104-148	121, 100-143

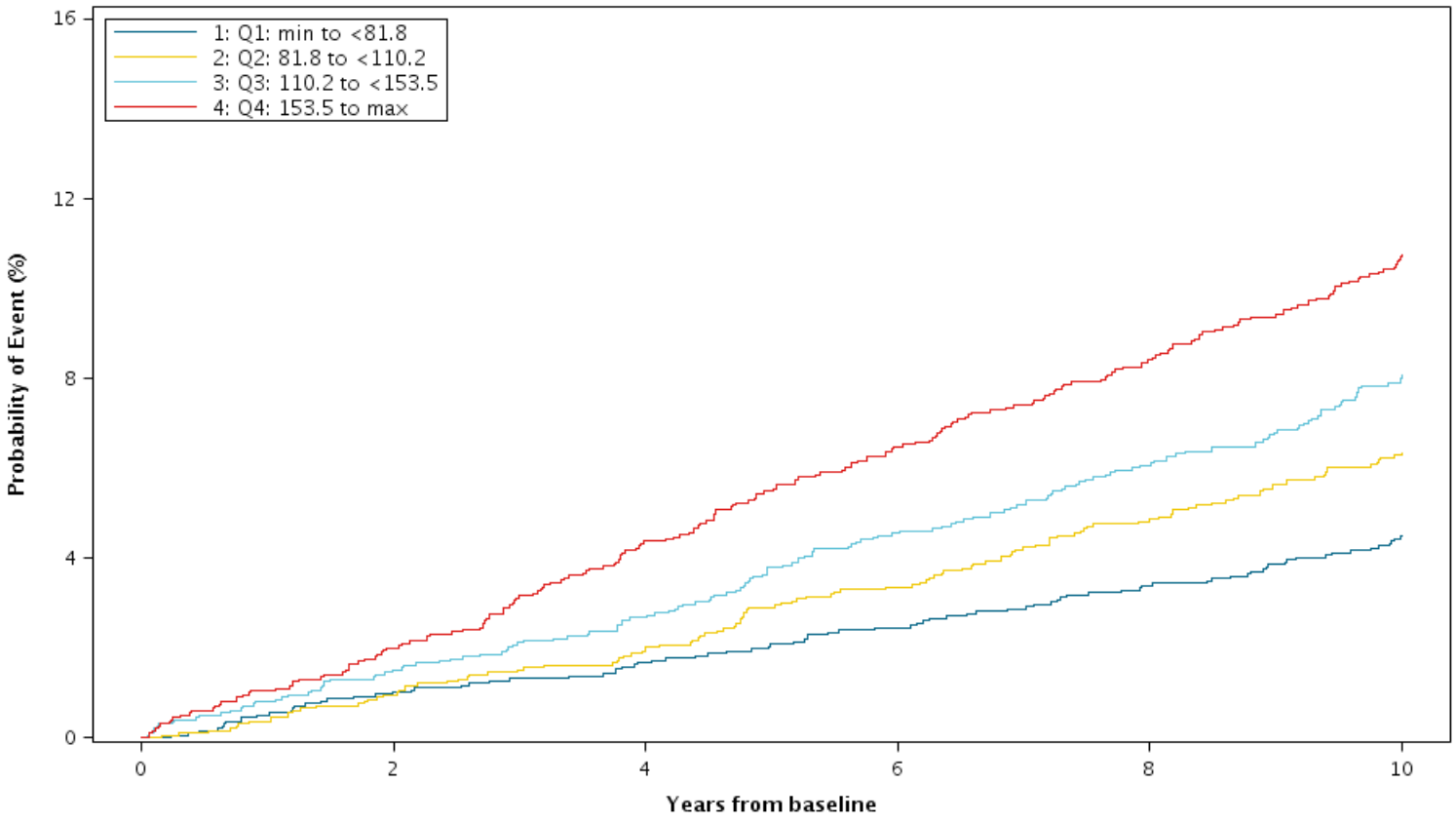
Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

Distribution of Triglycerides in the Studied Populations



Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

TG-CVD Association was Strongest for Average TGs



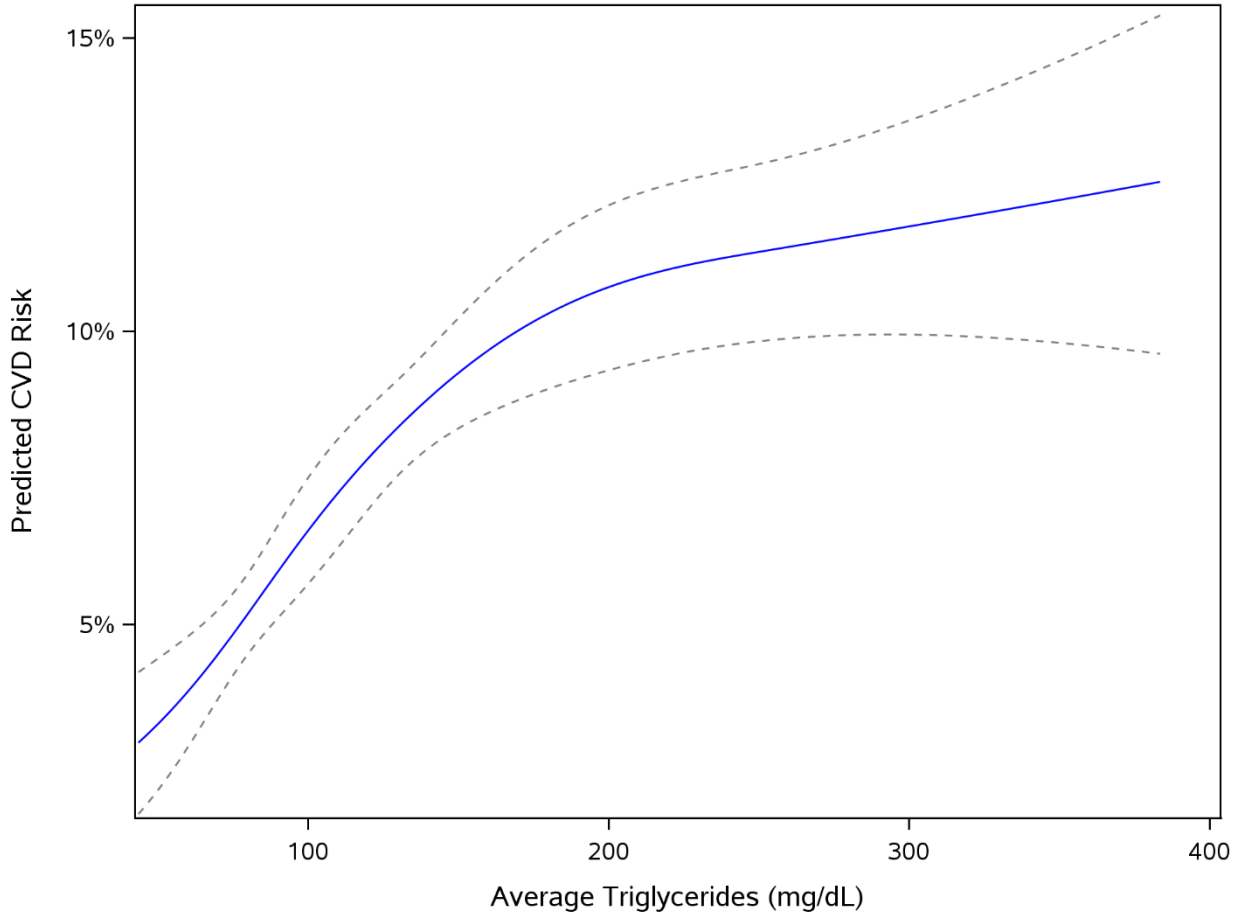
Number at risk:

1	1981	1956	1926	1885	1855	1798
2	1995	1967	1918	1873	1817	1755
3	1998	1956	1916	1860	1807	1729
4	2004	1954	1888	1807	1736	1657

Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

Direct Association between Average TG and CVD

CVD increased across the entire range of TG levels to around 150 mg/dL, above which the relationship flattened out



Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

95% confidence intervals (dotted lines)

Subgroup Analysis of TG-CVD Relationship

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Significant interactions were found for women and those with high HDL-C

Interaction Examined	Hazard Ratio (95% CI)	Interaction P Value
Sex		0.014
Female	1.79 (1.50-2.14)	
Male	1.34 (1.15-1.55)	
HDL-C		0.014
At HDL=40 mg/dL	1.32 (1.13-1.53)	
At HDL=50 mg/dL	1.55 (1.29-1.86)	
At HDL=60 mg/dL	1.68 (1.37-2.06)	

Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

Key Takeaways Regarding TGs as a Marker of Risk

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Conclusions

- Assessment is better using average of 2+ TG measurements
- Increasing TGs are associated with increased risk of CVD, particularly in women
- TGs <100 mg/dL are still associated with CVD risk
- Data suggests that 150 mg/dL is threshold to identify adults with the highest TG-related risk

Navar AM, Pagidipati N, Mulder H. ACC 2019, New Orleans.

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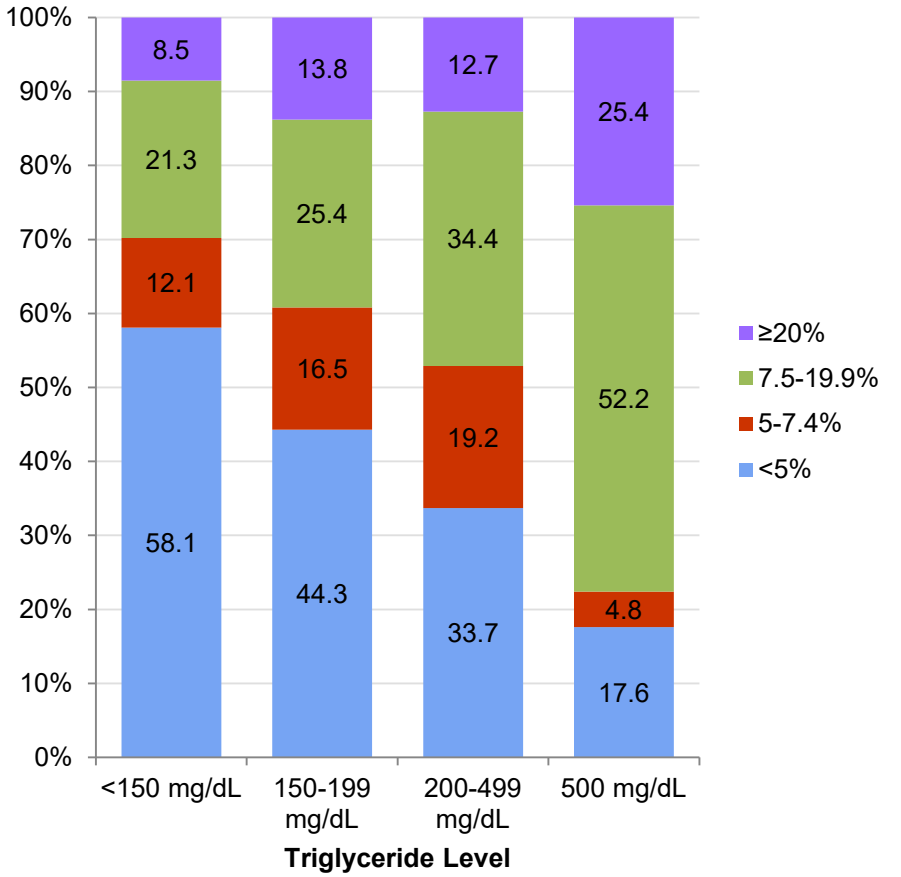
Estimating Risk in the US Population

- More than one-fourth of US adults have HTG[1]
- Despite stain use, many adults still have HTG[1]
- *Burden of Atherosclerotic Cardiovascular Disease Risk in Persons with Elevated Triglyceride Levels According to Statin Use*
  - Used NHANES 2007-2014 data to estimate 10-year ASCVD risk and events
    - For persons with and without HTG
    - According to statin use[2]

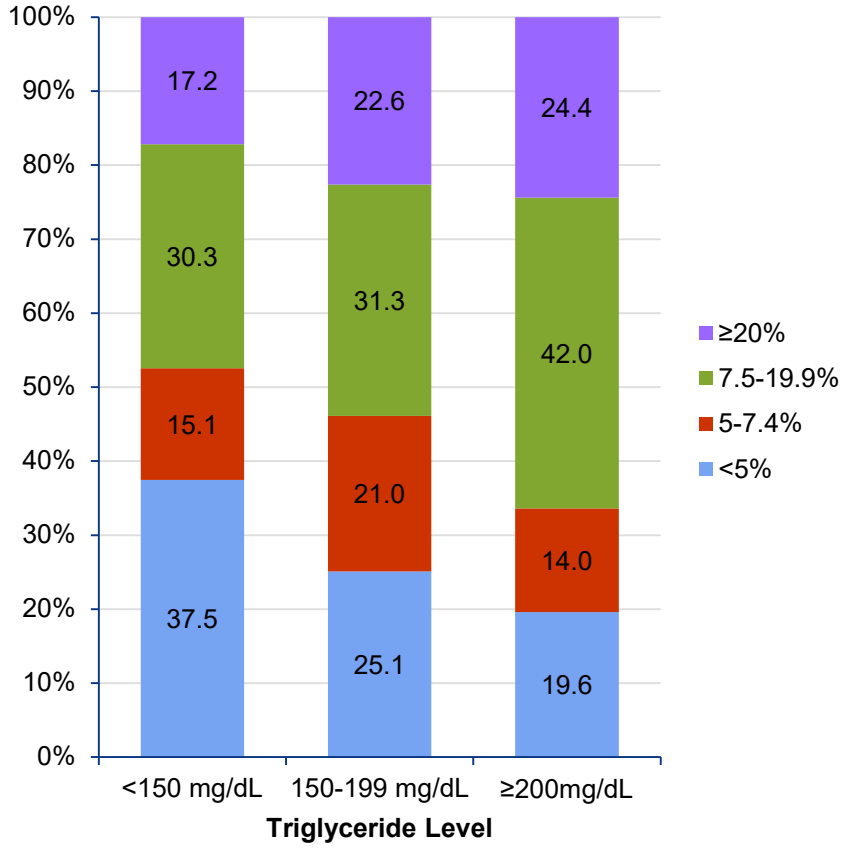
1. Fan W, et al. J Clin Lipidol. 2019;13 (1):100-108. 2. Wong ND, Fan W, Philip S. ACC 2019, New Orleans.

10-year Risk by TG Level with or without Statin Use

Proportions of US adults with different ASCVD risk score (%) levels by triglyceride group



Overall



On Statins

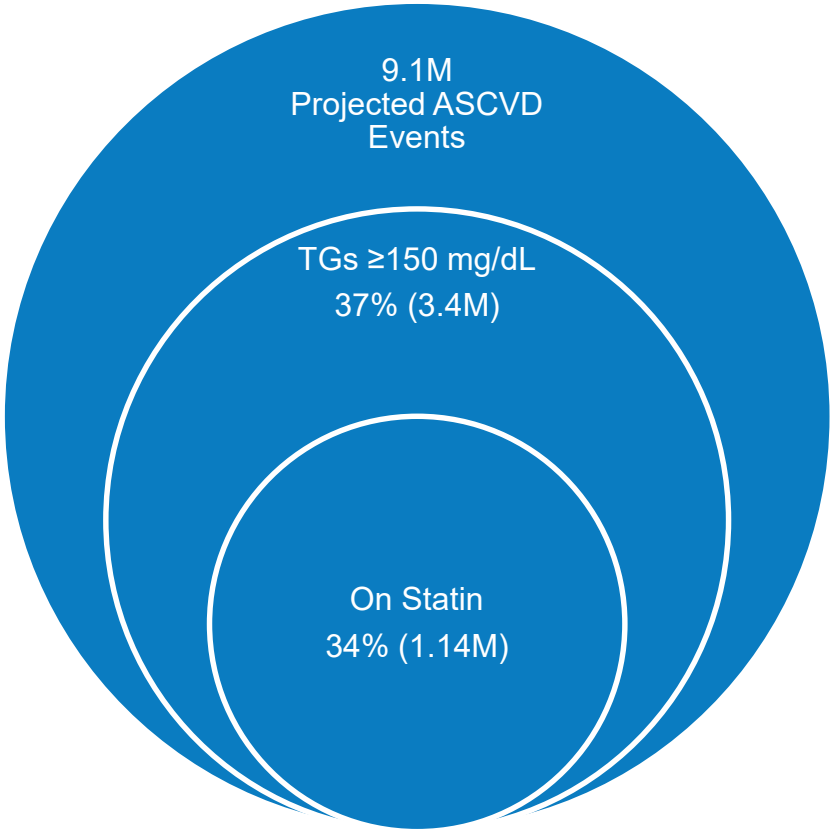
Wong ND, Fan W, Philip S. ACC 2019, New Orleans.

Who Among the US Population is at Risk?

Estimating Risk in the US Population

- Patients with high TGs have many other risk factors for CVD that drive risk
  - As TGs increase, so does risk
- >1 in 3 CV events projected to occur in adults with TGs ≥150 mg/dL

Projected CV Events



1. Fan W, et al. J Clin Lipidol. 2019;13 (1):100-108. 2. Wong ND, Fan W, Philip S. ACC 2019, New Orleans.

What Does This Mean in Terms of ASCVD Events?

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Limitations

- These analyses are restricted to primary prevention cohorts

Conclusions

- Over the next 10 years >3M ASCVD events are expected in those with TG ≥150 mg/dL
- Approximately 1 million events are expected in statin users
- Emphasis is needed on:
  - Nutritional and physical activity counseling
  - Newer therapies that address HTG beyond statin therapy

Increased Residual Cardiovascular Risk in U.S. Veterans with Moderately-Elevated Baseline Triglycerides and Well-Controlled LDL-C on Statins

William E. Boden, MD, FACC, FAHA
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Disclosures

Dr. William Boden discloses the following relationships - Research grant support: Clinical Trials Network, Massachusetts Veterans Epidemiology, Research, and Information Center, VA New England Healthcare System; National Heart, Lung, and Blood Institute as National co–principal investigator for the ISCHEMIA trial; Axio Research, Inc, Seattle, WA; AbbVie; Amarin Pharmaceuticals, Inc; Amgen; AstraZeneca; and Sanofi Aventis. Board of directors: Boston VA Research Institute, Inc and CardioDx, Mountain View, CA. Data monitoring committee: VA Cooperative Studies Program; national coordinator, STRENGTH trial, with honoraria from the Cleveland Clinic Clinical Coordinating Center. Speaking honoraria: Amgen; Aralez Pharmaceuticals; AstraZeneca; and Regeneron

Can The Event Projections be Validated in Other Populations and Healthcare Systems?

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Background

- Retrospective Analysis of the National VA Corporate Data Warehouse (2010-2015)
  - Assessed
    - Number of statin-treated patients with elevated TGs (150-500 mg/dL) and well-controlled LDL-C (40-100 mg/dL)
    - CV event rates (nonfatal MI, stroke, unstable angina, or coronary revascularization) for elevated TG (150-500 mg/dL) vs normal TG (<150 mg/dL) groups during a 5-year follow-up

Key Baseline Characteristics of the VA Population Studied (n=439,019)

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	Elevated TG (n=132,203)	Normal TG (n=306,816)	
Baseline Characteristics			***P Value***
Age, yrs	72.3 ± 10.3	76.6 ± 9.8	<0.0001
Male (%)	98.2	98.6	<0.0001
Race (%)			<0.0001
White	79.9	73.9	
Black/A-A	5.7	9.8	
All Other	14.4	16.3	

Reporting mean +/- SD unless otherwise noted

Key Baseline Characteristics of the VA Population Studied (n=439,019)

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	Elevated TG (n=132,203)	Normal TG (n=306,816)	
Baseline Characteristics			***P Value***
Statin Intensity (%)			<0.0001
High	51.5	49.0	
Moderate	35.0	43.0	
Low	13.5	8.1	
BMI, kg/m^2	33.3 ± 1.7	30.0 ± 1.0	0.0961
Systolic BP, mmHg	132.2 ± 19.1	130.8 ± 19.1	<0.0001
Diastolic BP, mmHg	71.6 ± 11.8	70.1 ± 11.7	<0.0001

Reporting mean +/- SD unless otherwise noted

Key Baseline Characteristics of the VA Population Studied (n=439,019)

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	Elevated TG (n=132,203)	Normal TG (n=306,816)	
Baseline Characteristics			***P Value***
Total Cholesterol, mg/dL	162.3 ± 32.4	141.8 ± 26.9	<0.0001
LDL-C, mg/dL	81.3 ± 26.5	78.2 ± 21.3	<0.0001
HDL-C, mg/dL	36.3 ± 10.0	44.7 ± 14.1	<0.0001
Triglycerides, mg/dL	223.6 ± 74.0	94.4 ± 31.6	<0.0001
eGFR (% >60 ml/min)	96.7	70.0	<0.0001
HbA1c, %	7.2 ± 1.5	6.7 ± 1.5	<0.0001
Follow-up duration, yrs	3.6 ± 1.6	3.4 ± 1.6	<0.0001

Reporting mean +/- SD unless otherwise noted

Key Baseline Characteristics of the VA Population Studied (n=439,019)

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	Elevated TG (n=132,203)	Normal TG (n=306,816)	
Unadjusted Outcomes			***Rate Ratio (95% CI)***
Composite CV outcome	11239 (8.5%)	19290 (6.3%)	1.37 (1.34, 1.40)
Individual CV end points			
Non-fatal MI	6370 (4.8%)	10672 (3.5%)	1.39 (1.34, 1.43)
Non-fatal stroke	2743 (2.1%)	5277 (1.7%)	1.21 (1.15, 1.26)
Coronary revascularization	1285 (1.0%)	1708 (0.6%)	1.75 (1.62, 1.88)
Unstable angina	2379 (1.8%)	3362 (1.1%)	1.64 (1.56, 1.73)

Reporting mean +/- SD unless otherwise noted

Key Baseline Characteristics of the VA Population Studied (n=439,019)

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	Elevated TG (n=132,203)	Normal TG (n=306,816)	
Adjusted Outcomes			***Rate Ratio (95% CI)***
Composite CV outcome	11239 (8.5%)	19290 (6.3%)	1.19 (1.16, 1.22)
Individual CV end points			
Non-fatal MI	6370 (4.8%)	10672 (3.5%)	1.19 (1.15, 1.23)
Non-fatal stroke	2743 (2.07%)	5277 (1.7%)	1.08 (1.02, 1.14)
Coronary revascularization	1285 (1.0%)	1708 (0.6%)	1.41 (1.29, 1.53)
Unstable angina	2379 (1.8%)	3362 (1.1%)	1.38 (1.29, 1.46)

Reporting mean +/- SD unless otherwise noted

In the VA Population, Elevated TGs Meant More Events

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Results

- 30% of veterans had elevated TGs
- At baseline, the elevated TG group was:
  - Younger
  - Had a higher mean body mass index than the group with lower baseline TG
- The crude event rates for elevated TG vs normal TG groups
  - 1.37 (95% CI 1.34, 1.40; P<0.001)
- Adjusted* event rate for elevated TG vs normal TG groups
  - 1.19 (95% CI 1.16, 1.22; P<0.001)

*Adjusted for blood pressure, blood glucose levels, kidney function, and levels of HDL-C (“good cholesterol”)

What are the Implications?

Conclusions

- Patients with moderately-elevated TGs and well-controlled LDL-C had worse outcomes than patients with well-managed LDL-C levels and “normal” TG levels
- These findings are consistent with previous observational findings from other healthcare systems but in an older, sicker population for which TG-lowering therapy would be desirable

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REDUCE-IT™:
Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L. Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, John Gregson, PhD, Stuart J. Pocock, PhD, Christie M. Ballantyne, MD,
on Behalf of the **REDUCE-IT™** Investigators

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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,
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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

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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™**

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

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Independent Statistical Center Support for Data Monitoring Committee: Cyrus Mehta PhD, Rajat Mukherjee PhD

Clinical Endpoint Committee

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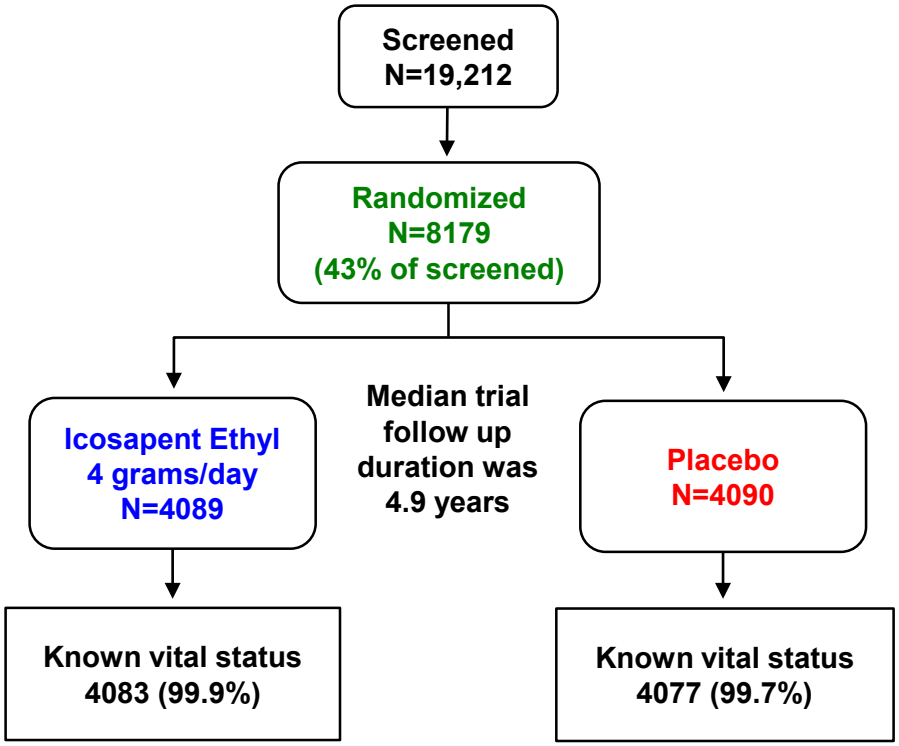
Independent Academic Statistical Analysis

Stuart J. Pocock PhD, John Gregson PhD

REDUCE-IT™ Design



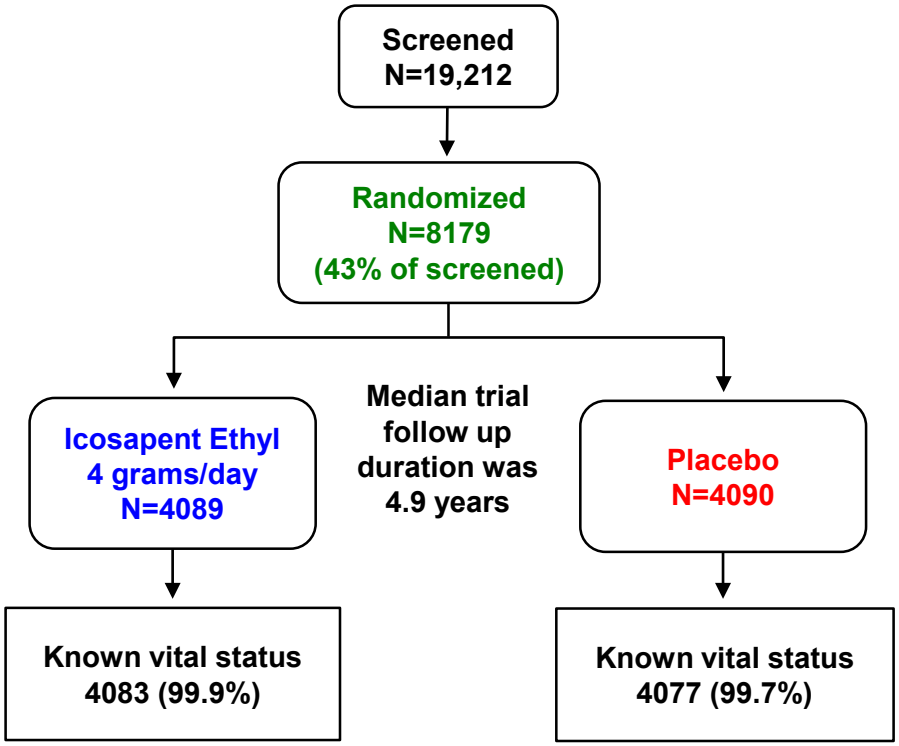
Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

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

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

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

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

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

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

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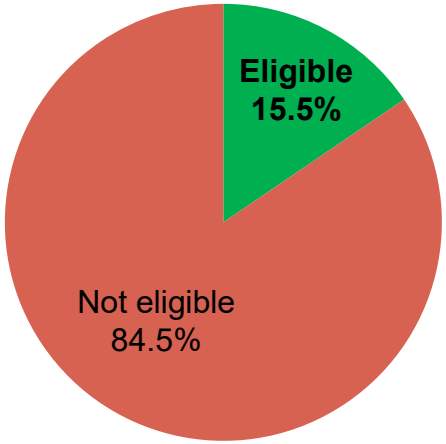
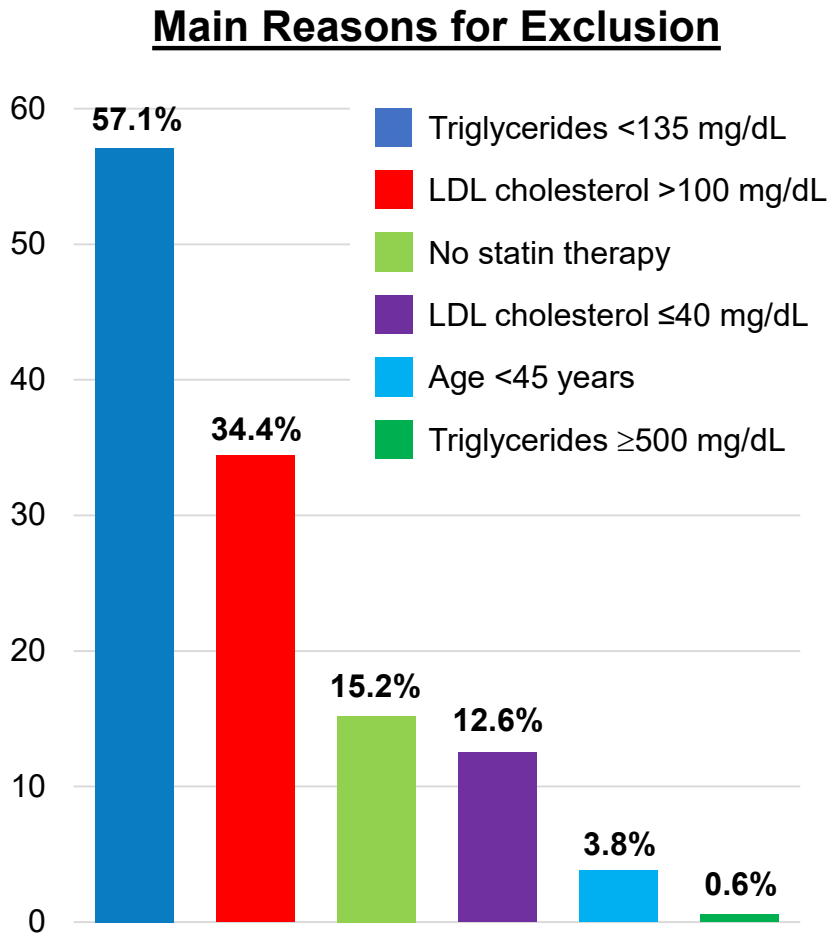
An analysis of 24,146 patients from the CLARIFY registry



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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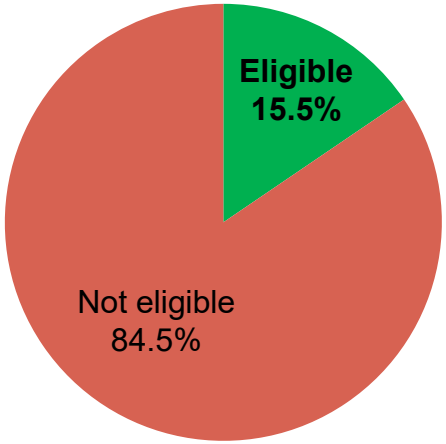

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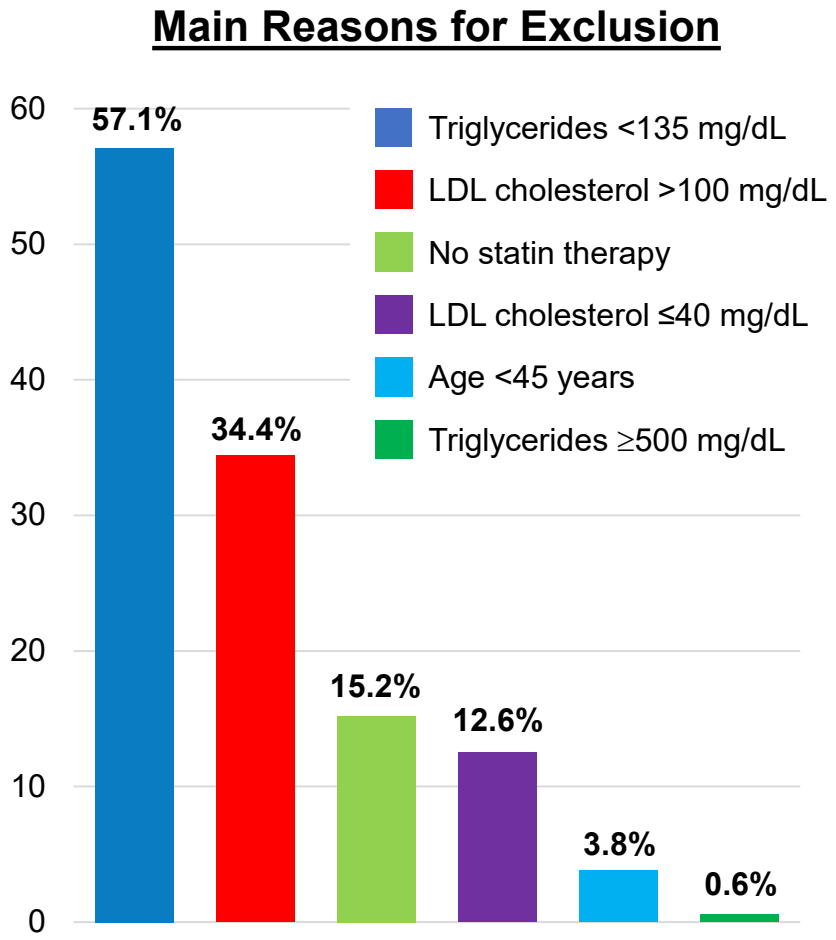
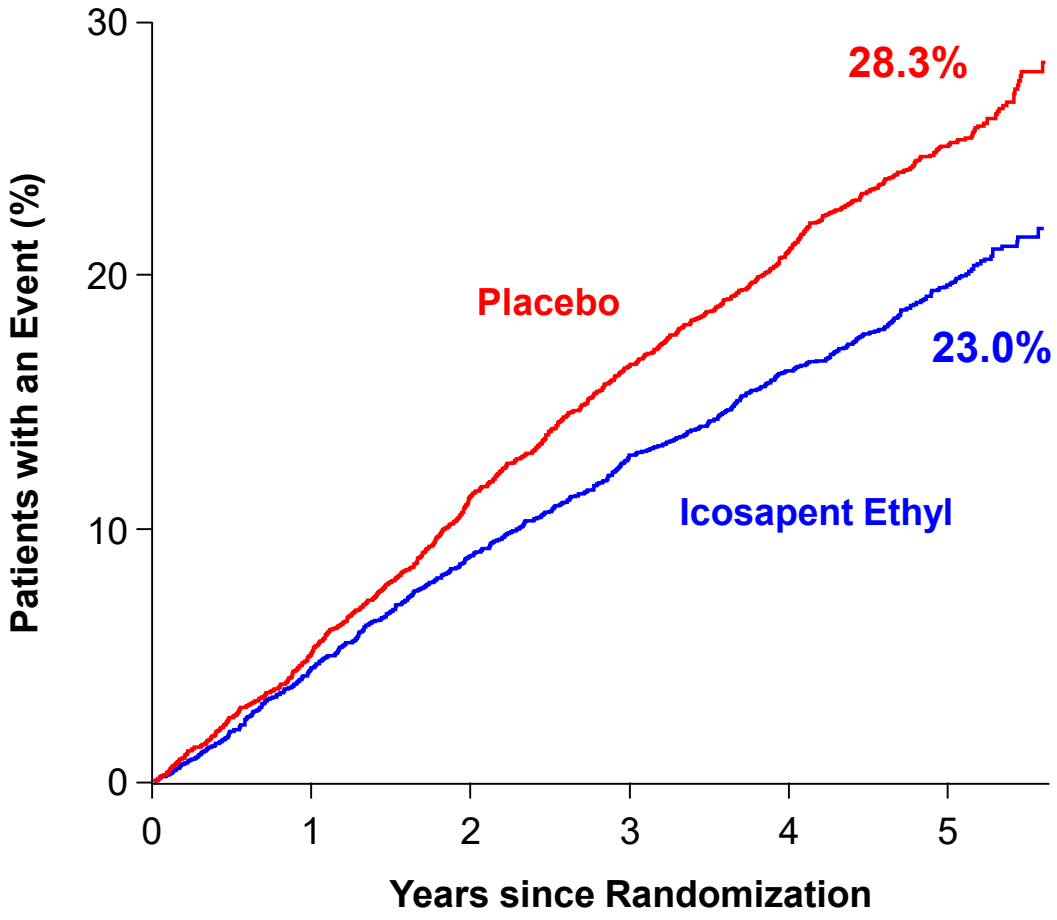
- AND triglycerides ≥135 and <500 mg/dL
- AND LDL-cholesterol >40 and ≤100 mg/dL

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%

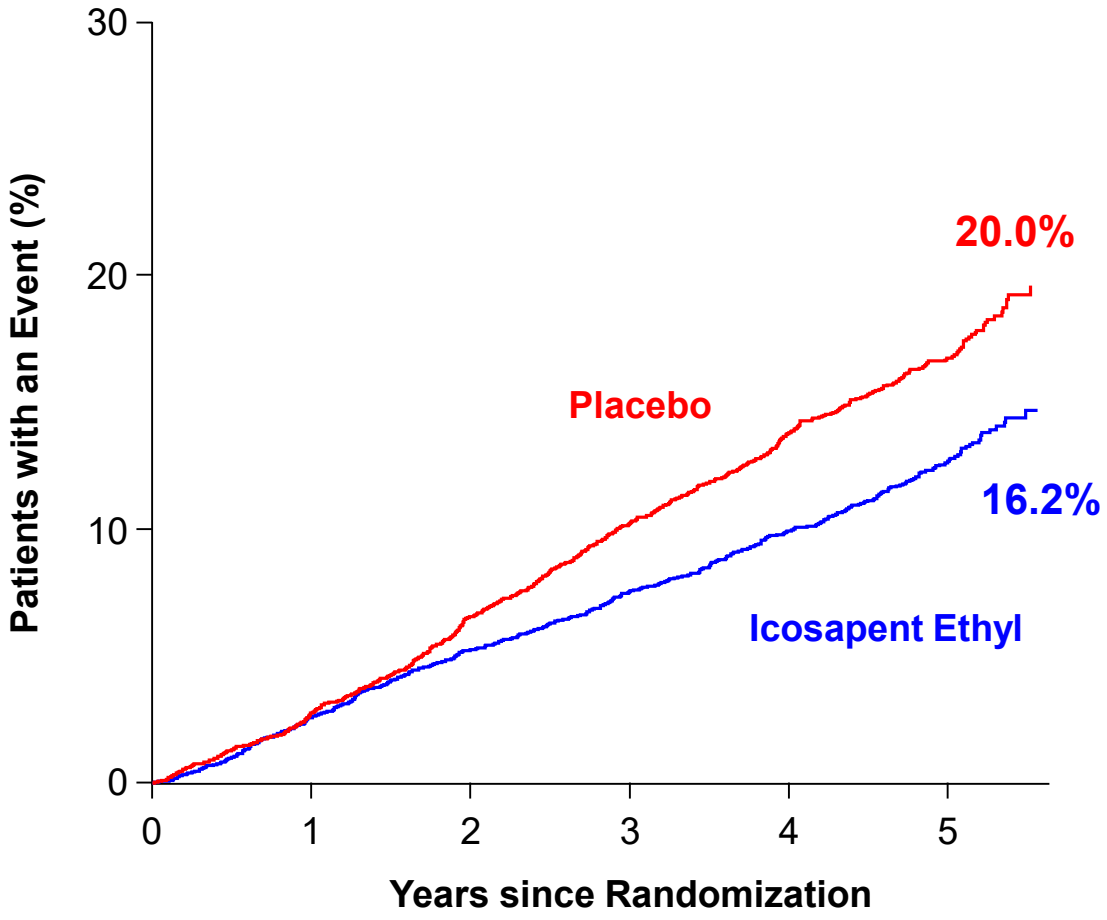
ARR = 4.8%

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%

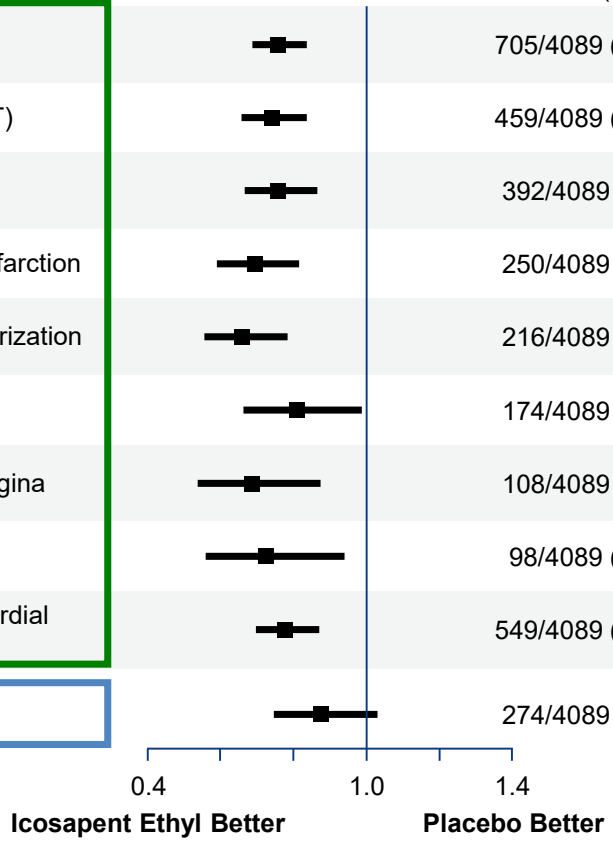
ARR = 3.6%

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 (pre-specified)
- Wei-Lin-Weissfeld with Li and Lagakos modification (prespecified)
- Joint-frailty *(post hoc)*

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

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.

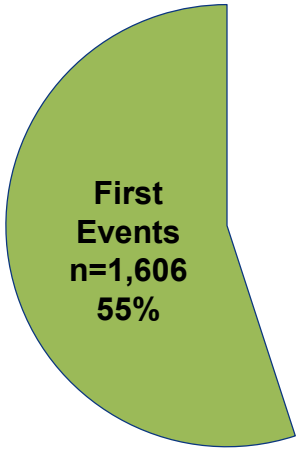
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019. Bhatt DL. ACC 2019, New Orleans.

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%)

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

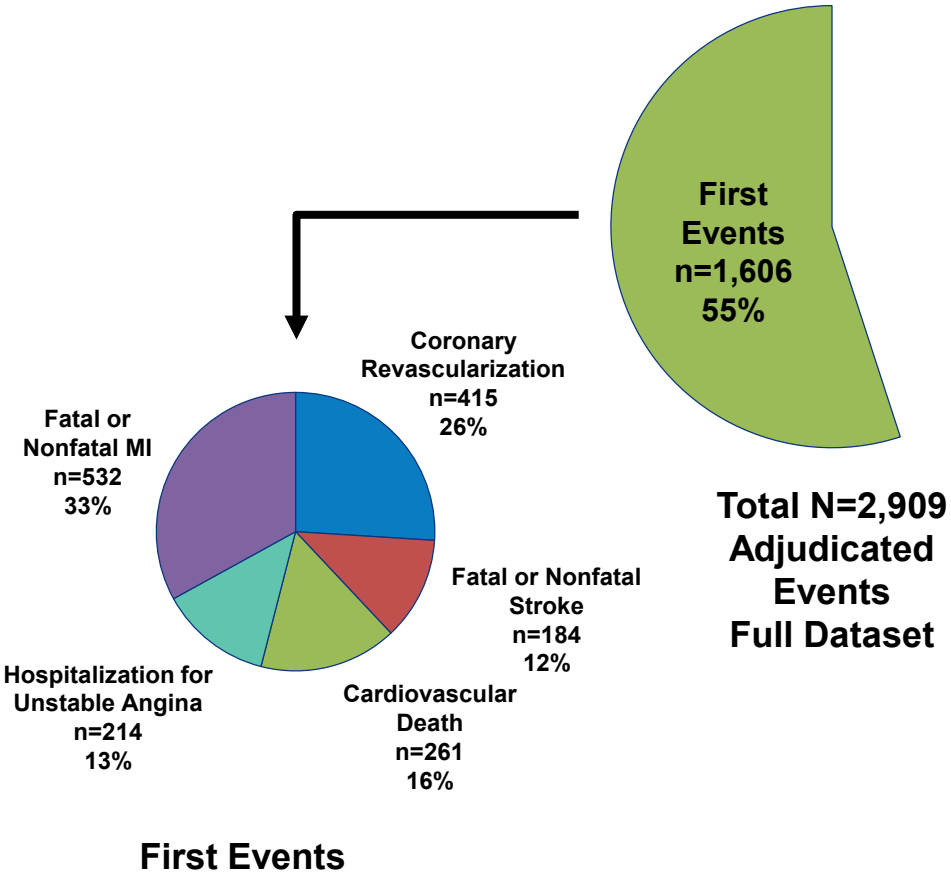
Proportions of First and Subsequent Events



Total N=2,909
Adjudicated Events
Full Dataset

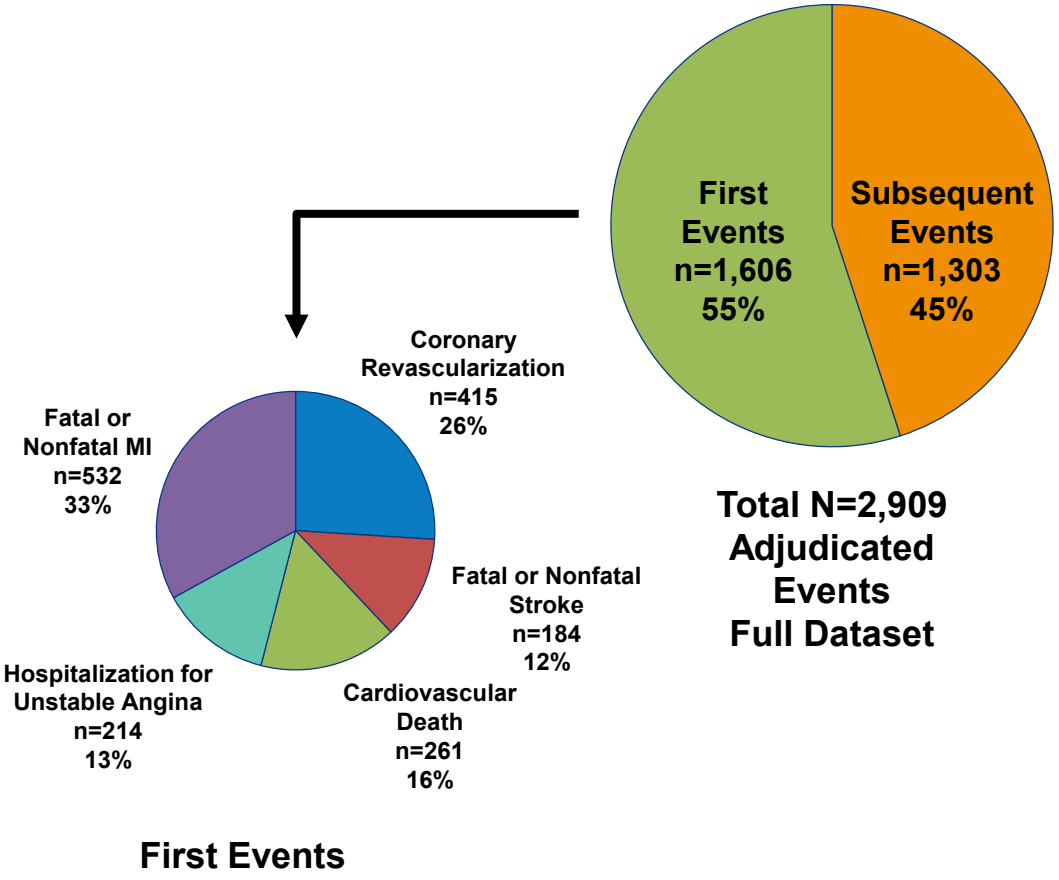
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

Proportions of First and Subsequent Events



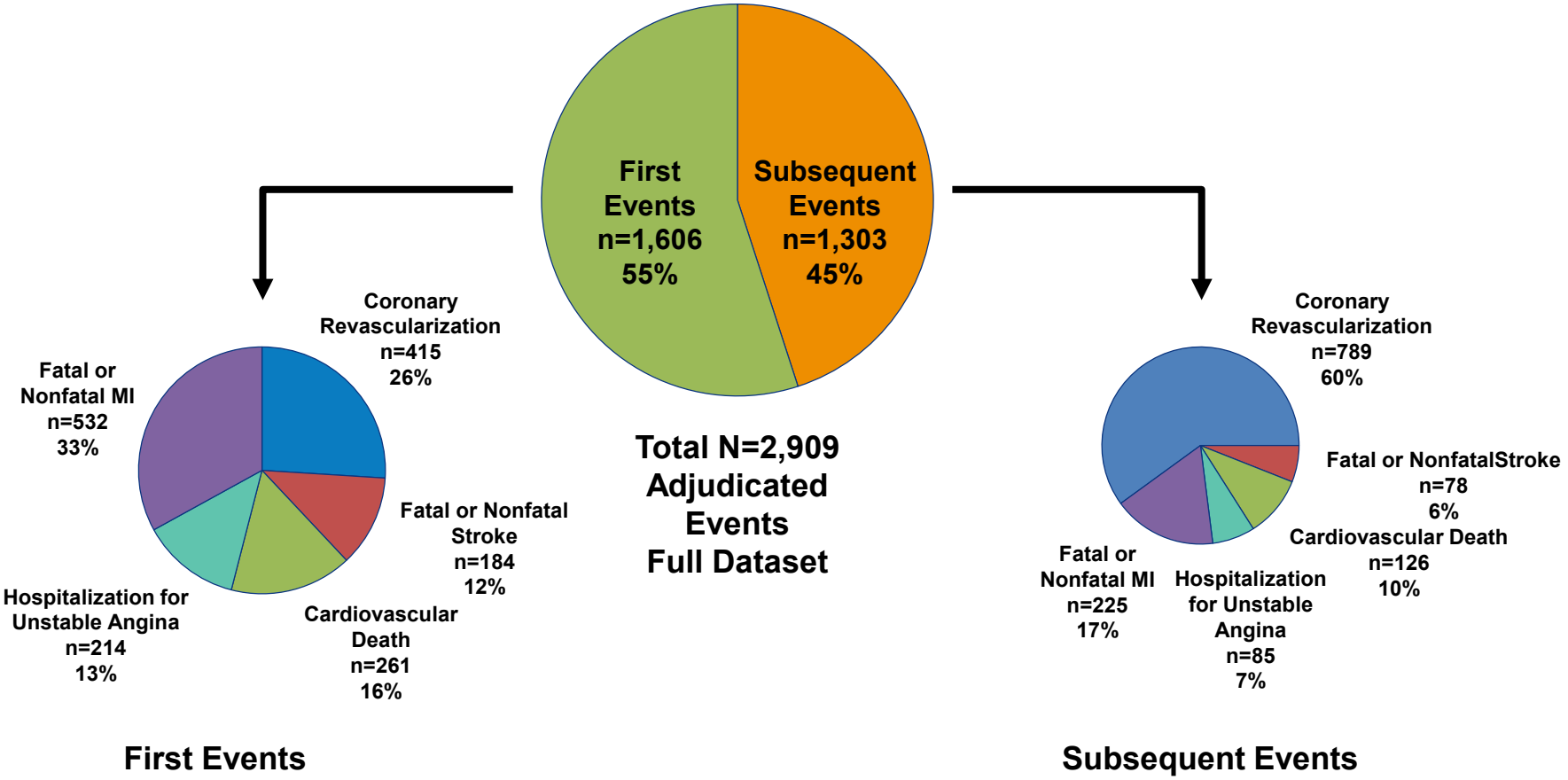
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

Proportions of First and Subsequent Events



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

Proportions of First and Subsequent Events



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

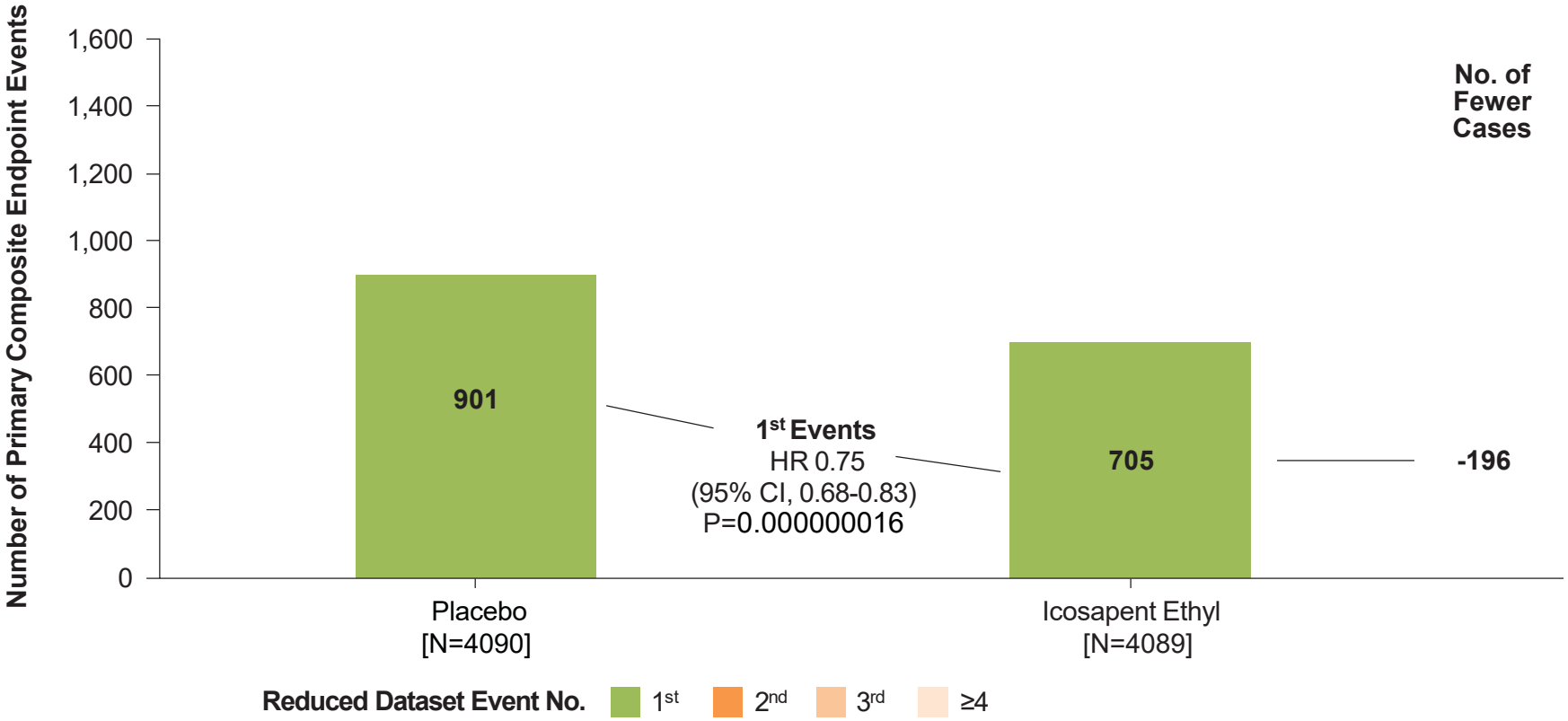
Event Counts

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"

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

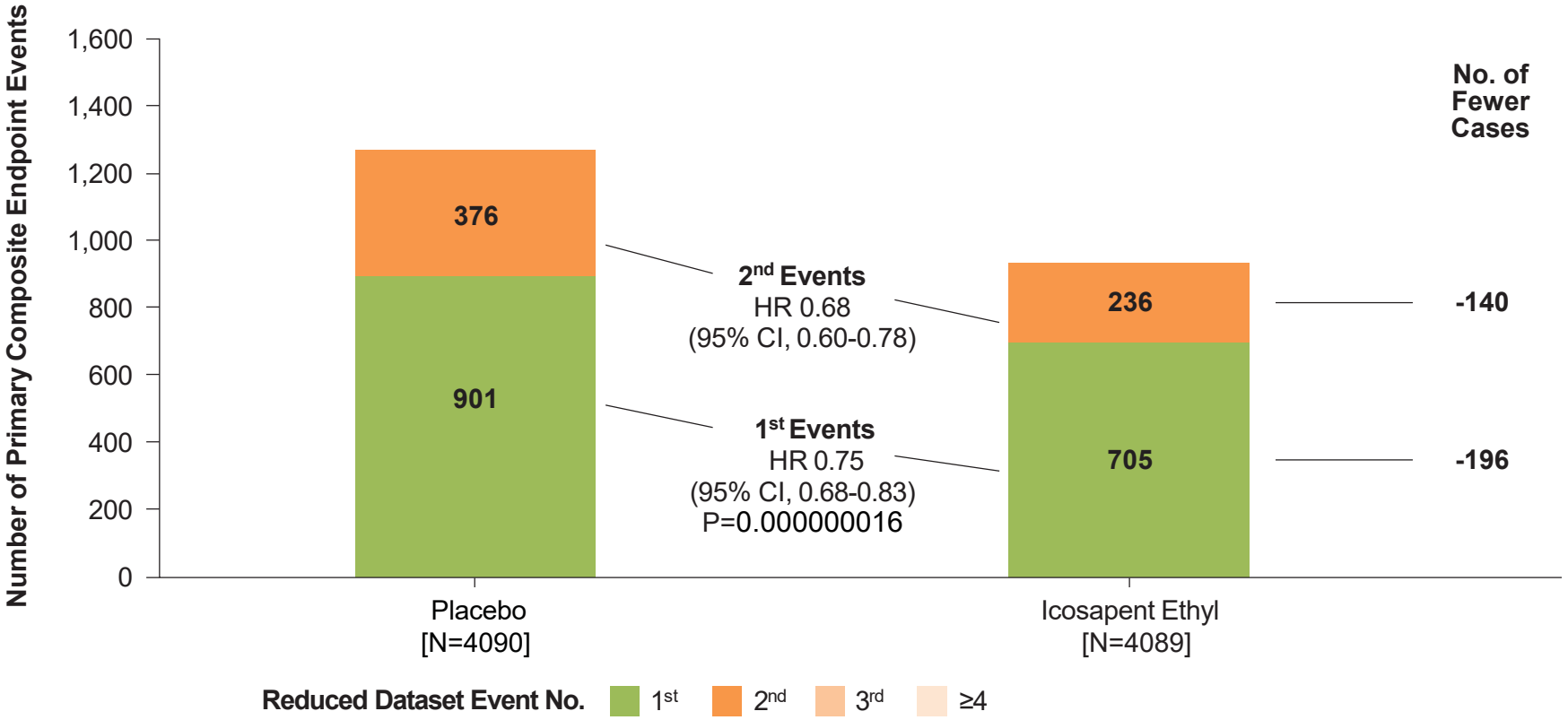
First and Subsequent Events



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

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

First and Subsequent Events



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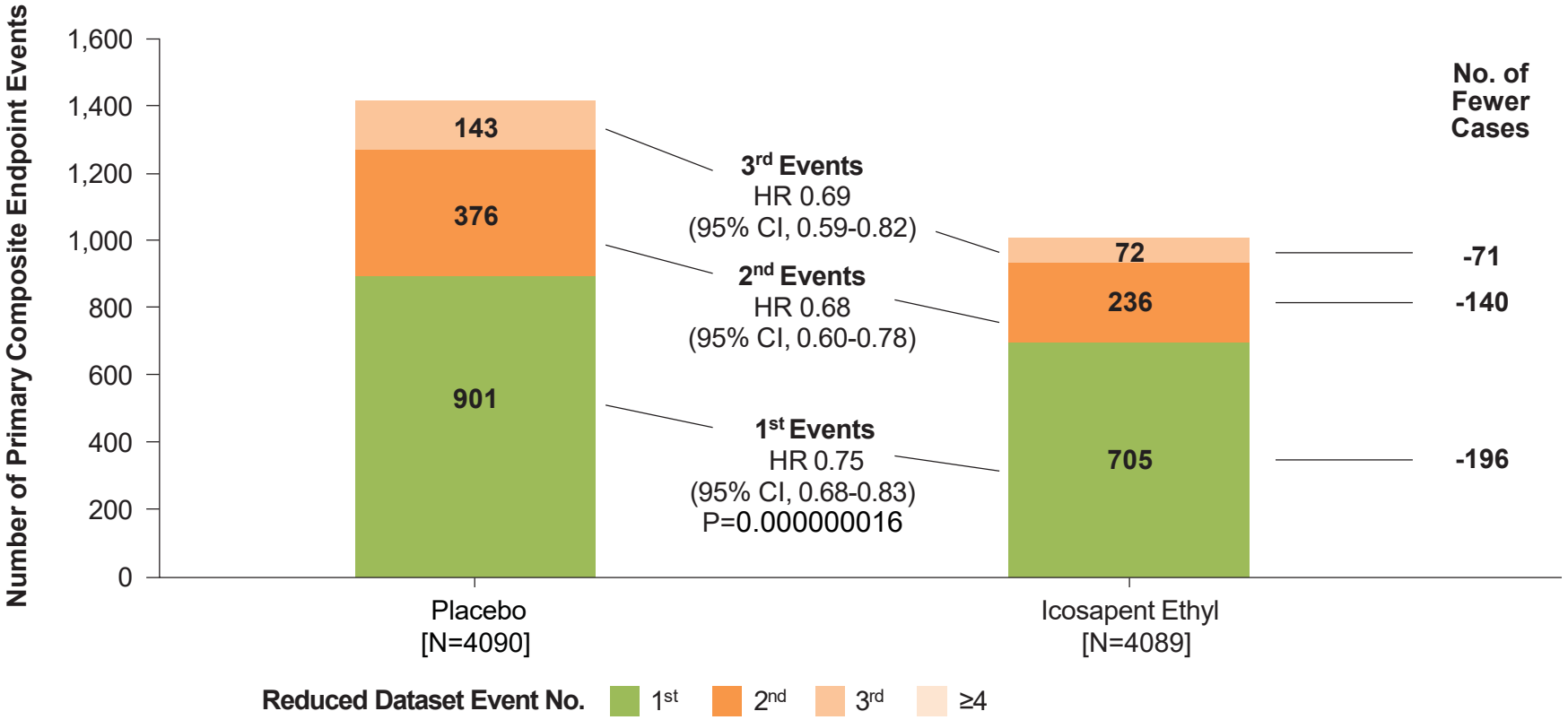
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

First and Subsequent Events



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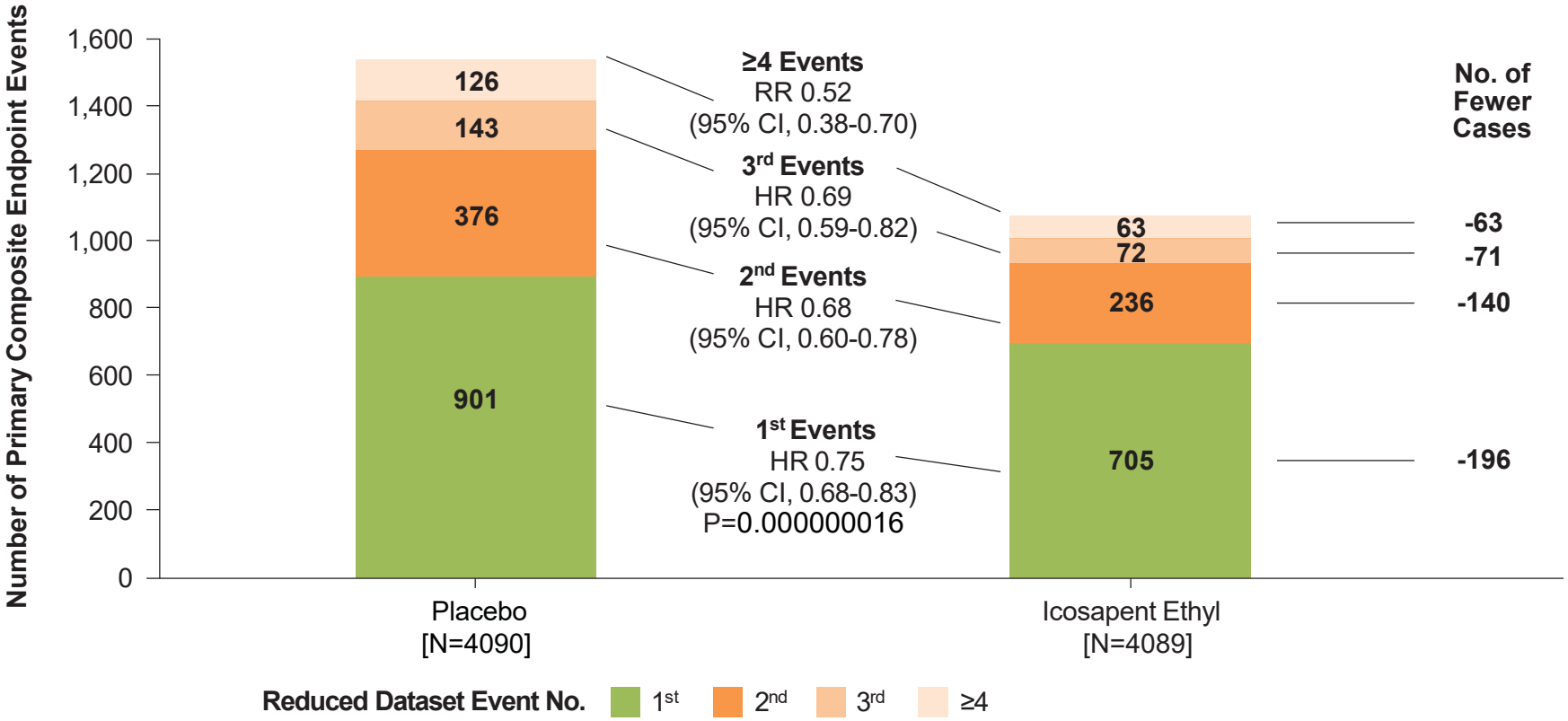
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

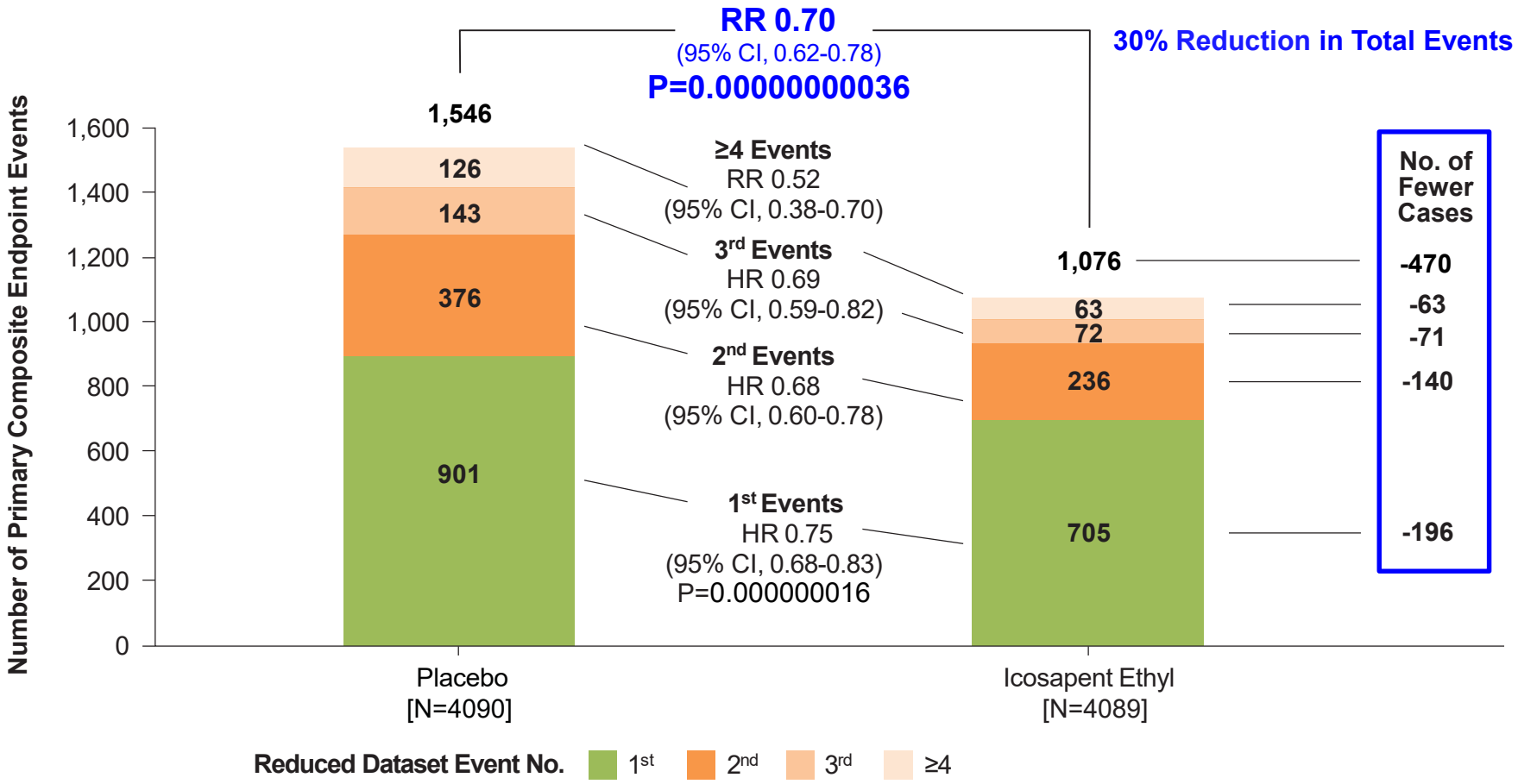
First and Subsequent Events



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

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

First and Subsequent Events

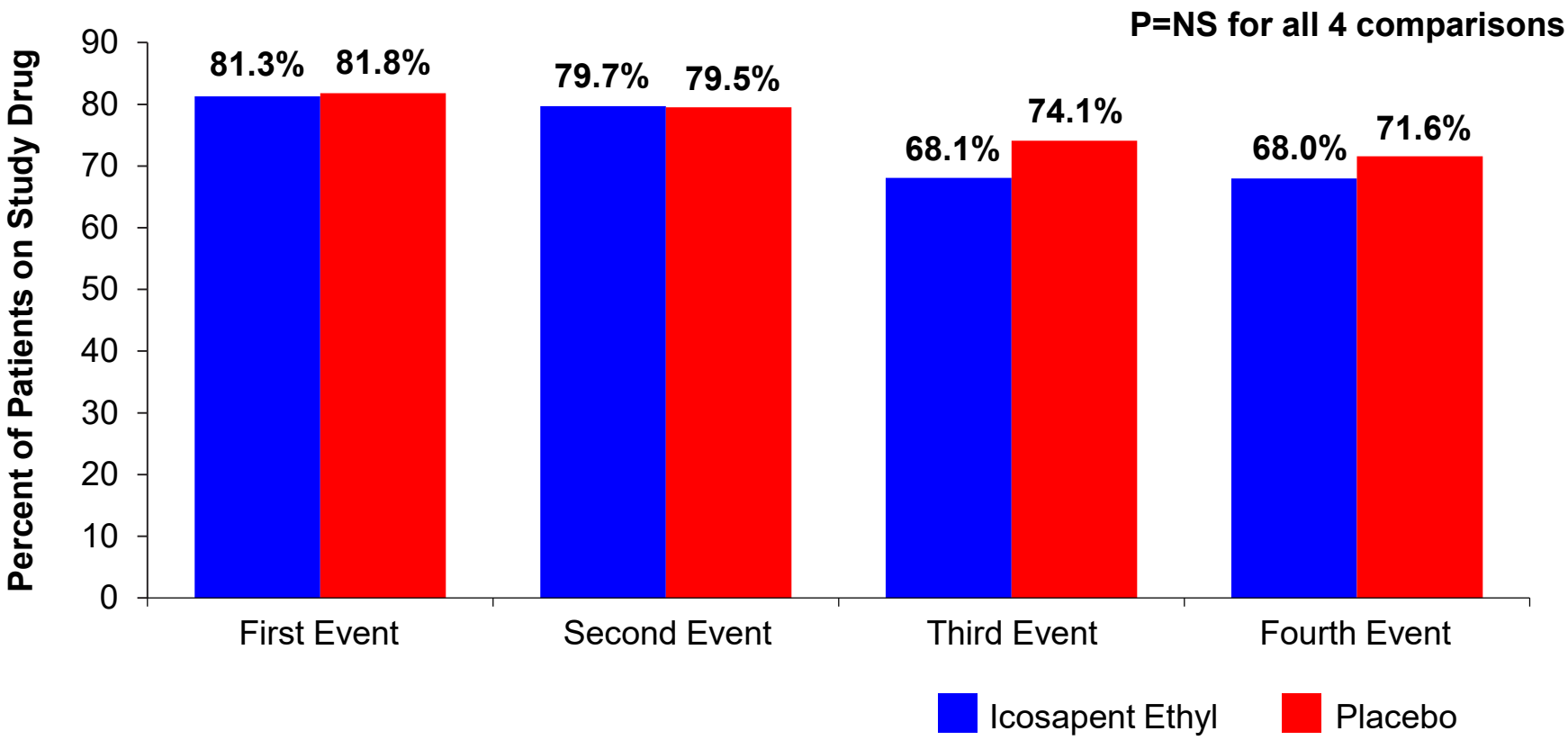


Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

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

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

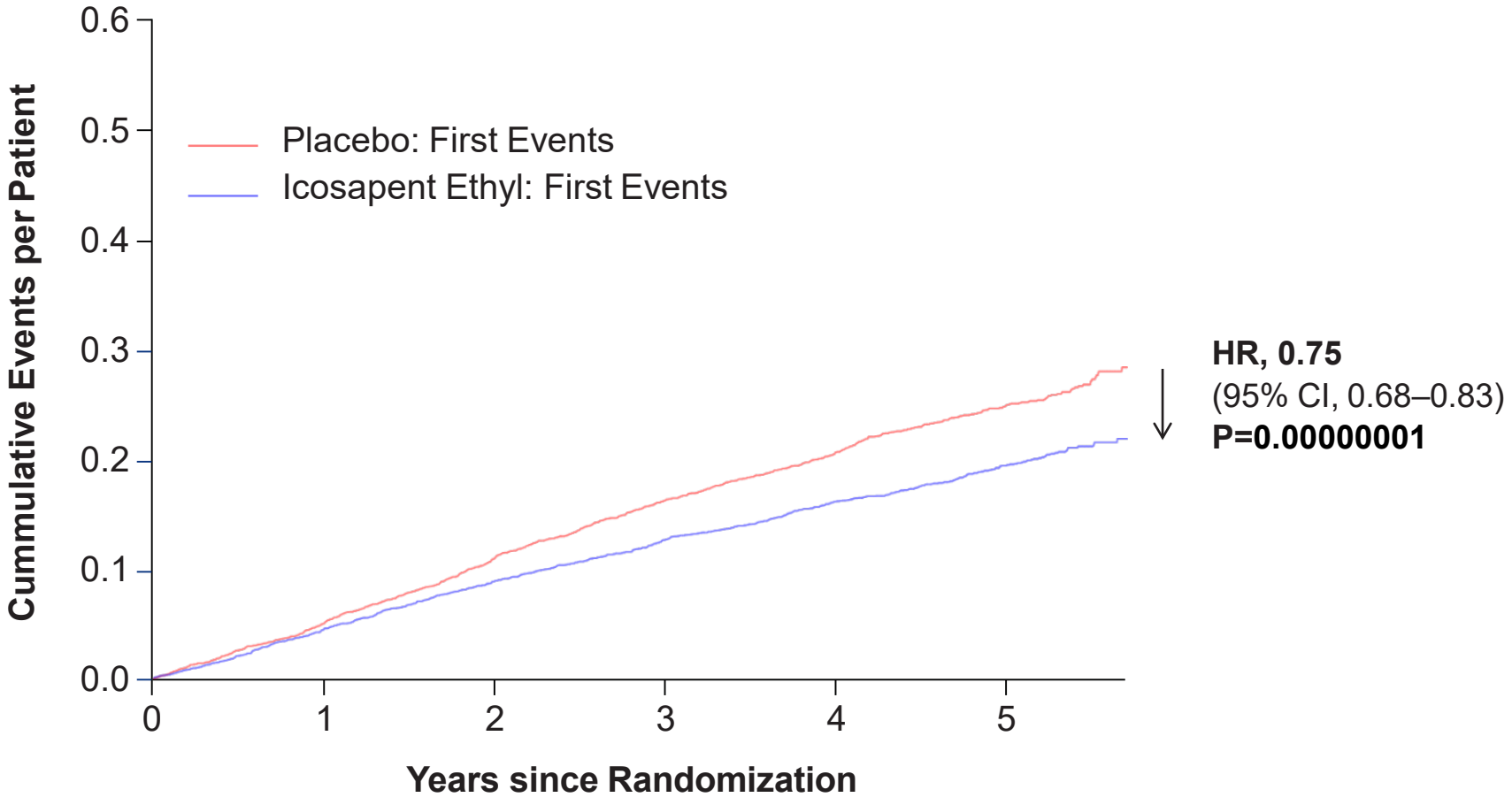


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019. Bhatt DL. ACC 2019, New Orleans.

Total (First and Subsequent) Events
Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

AMARIN

Primary Composite Endpoint



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

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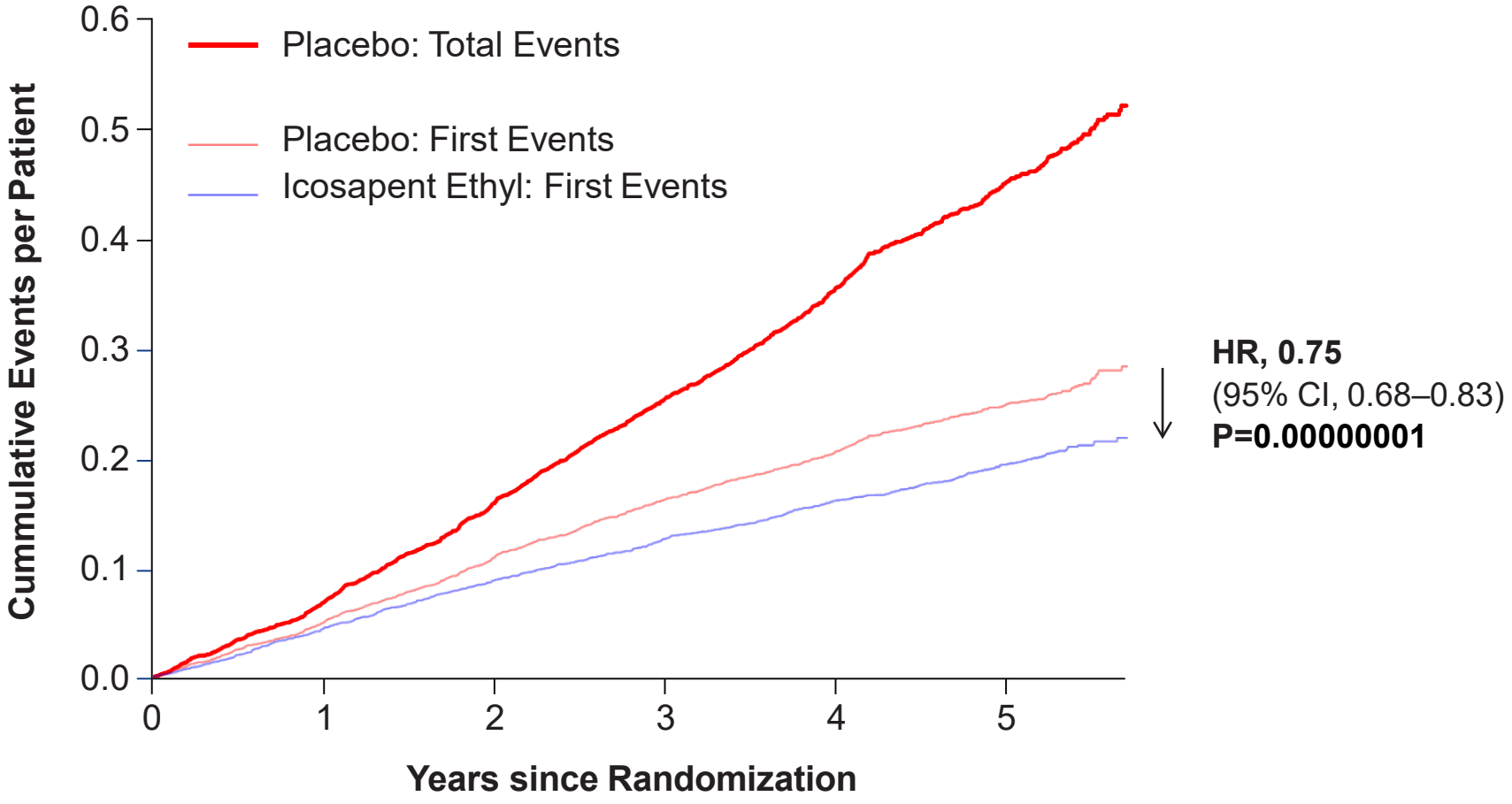
AMARIN

Primary Composite Endpoint



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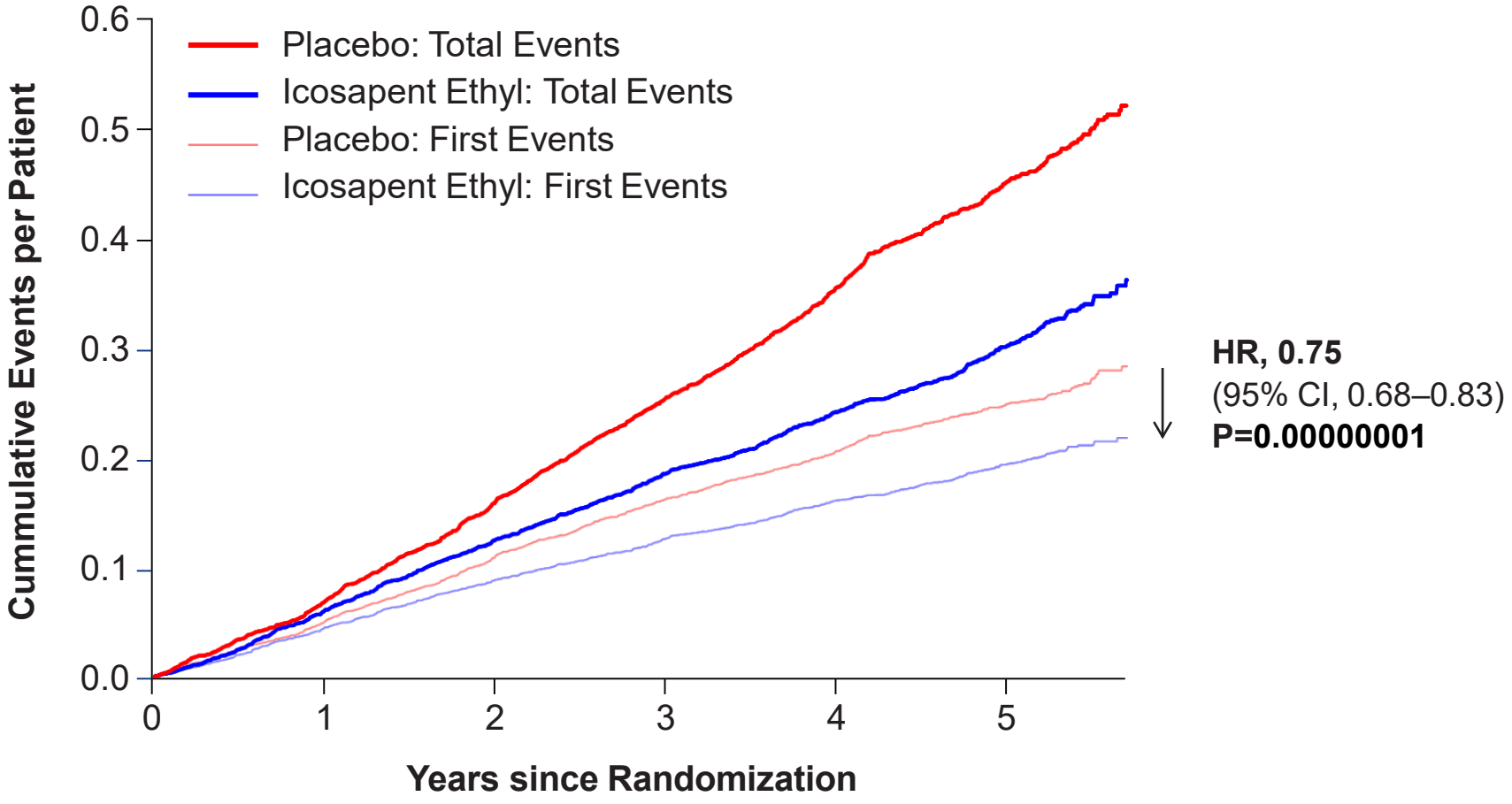
Primary Composite Endpoint



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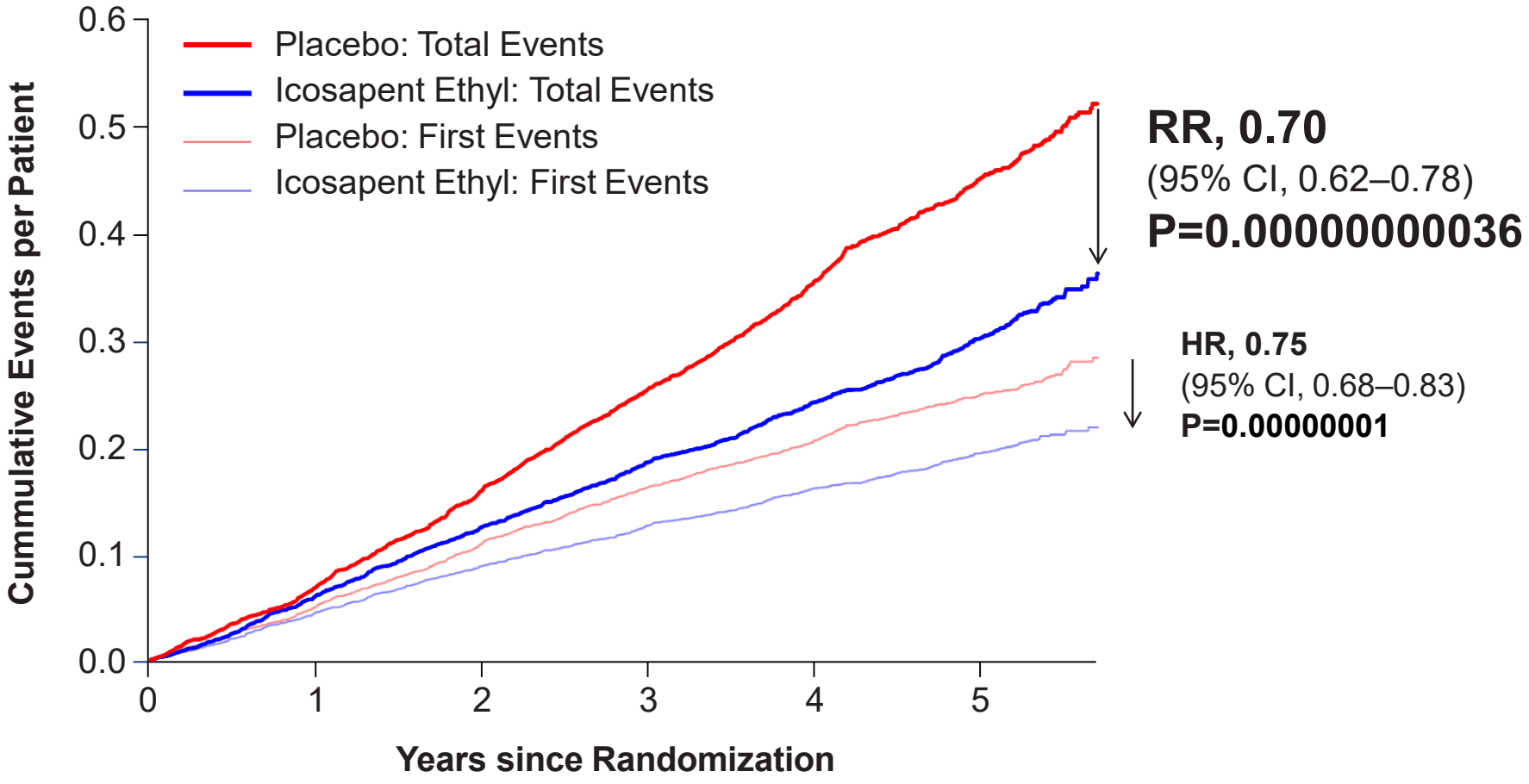
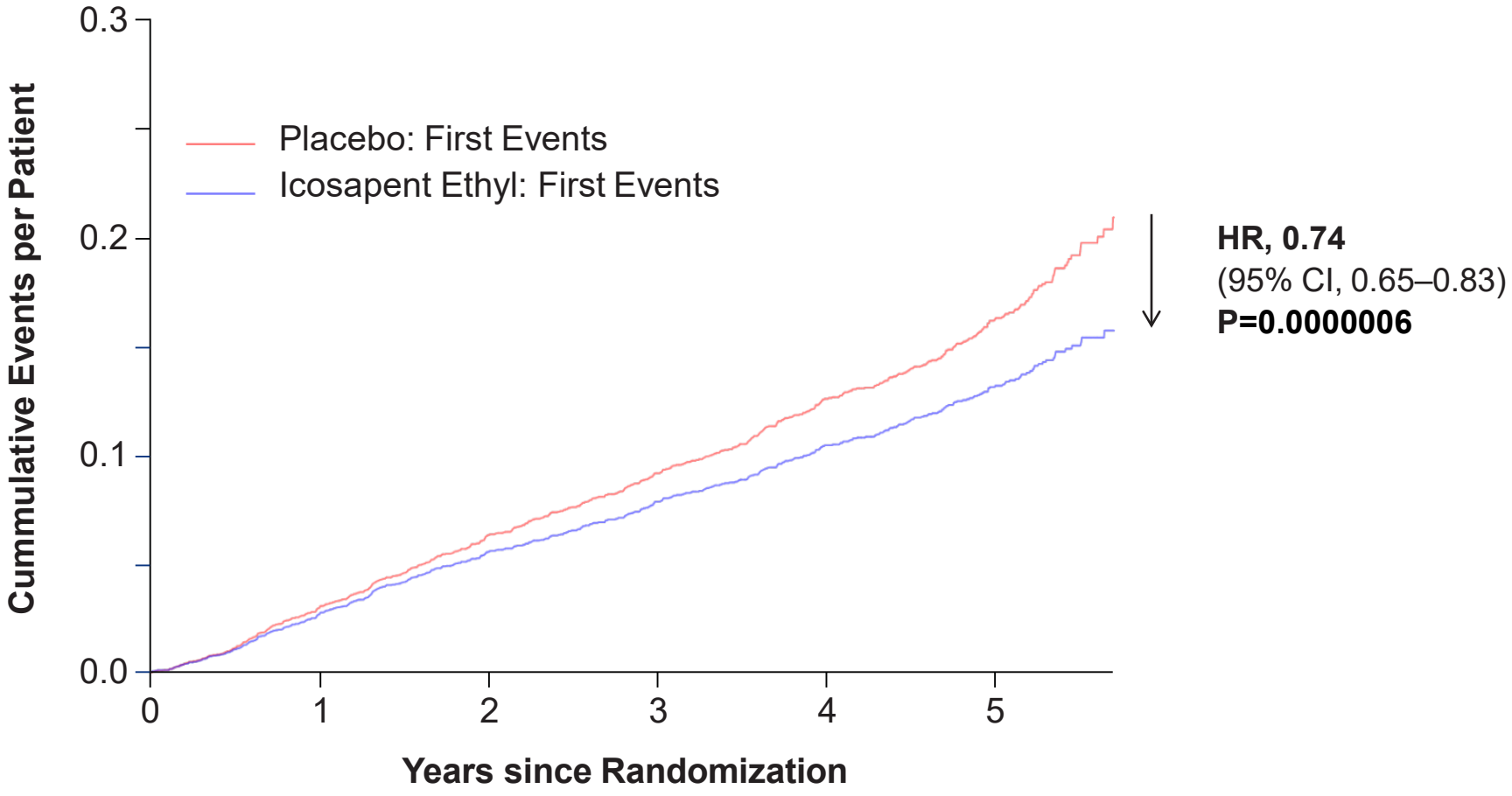


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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

Key Secondary Composite Endpoint

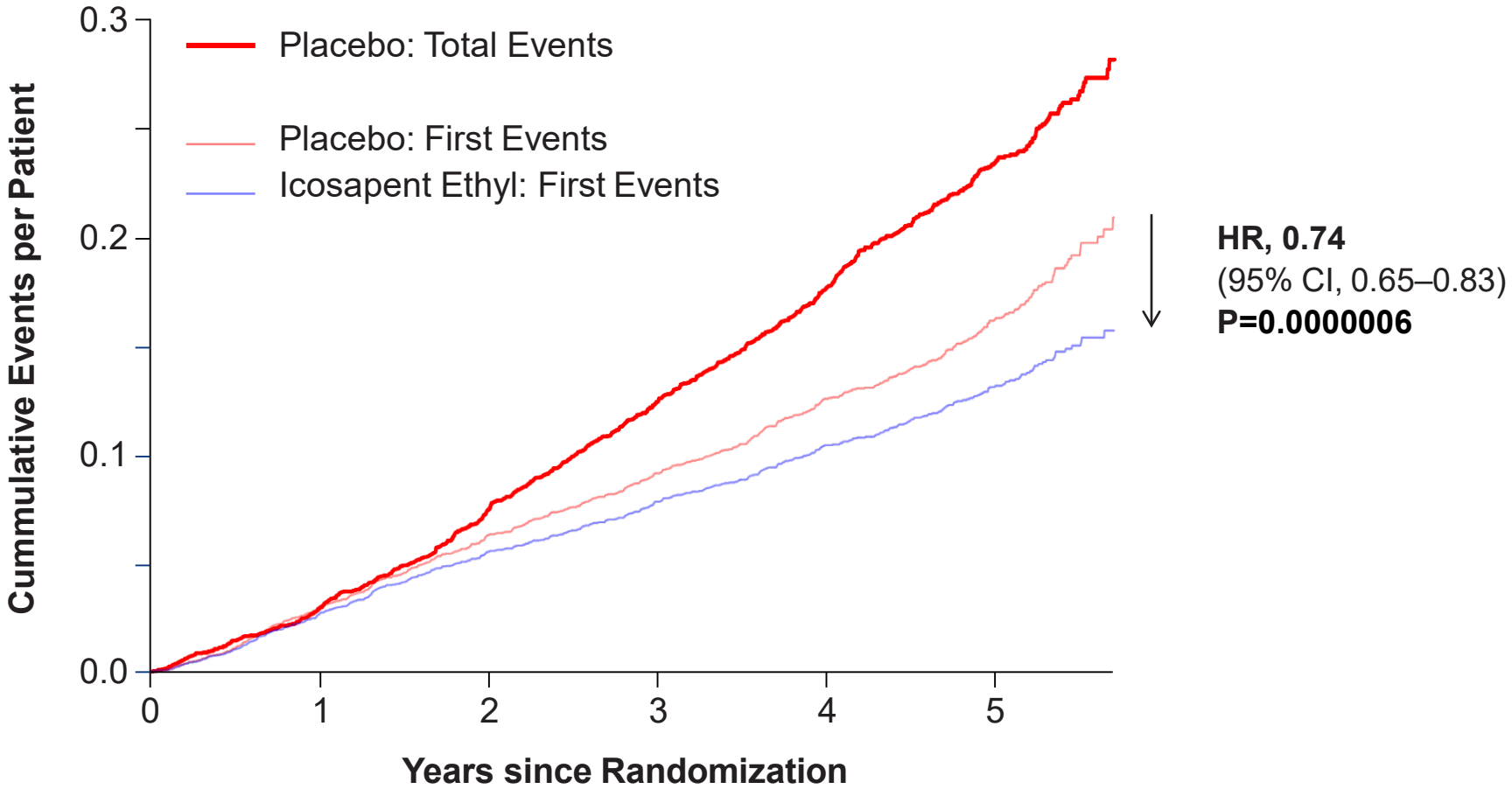


Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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

AMARIN

Key Secondary Composite Endpoint



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

Total (First and Subsequent) Events
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AMARIN

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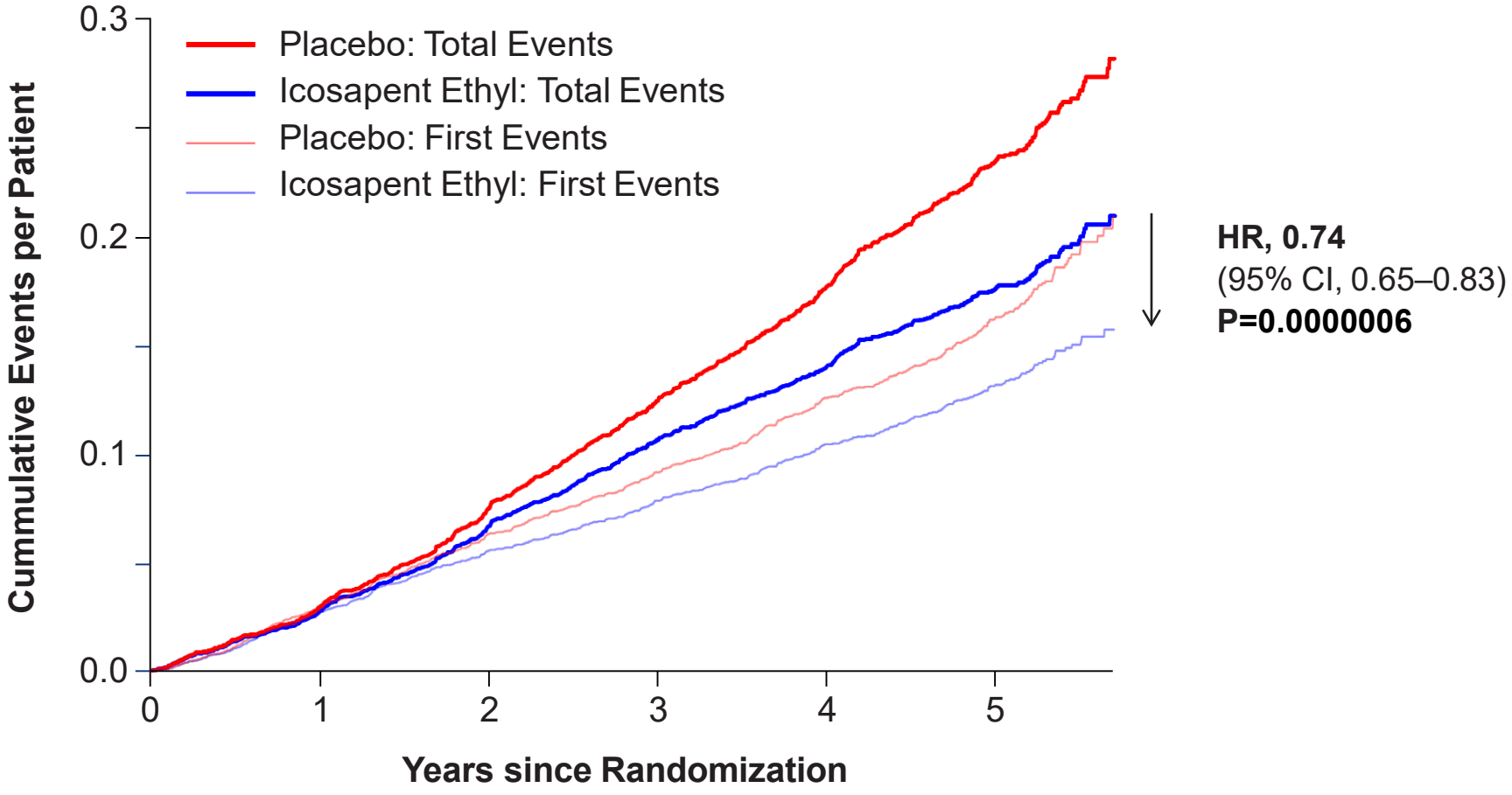

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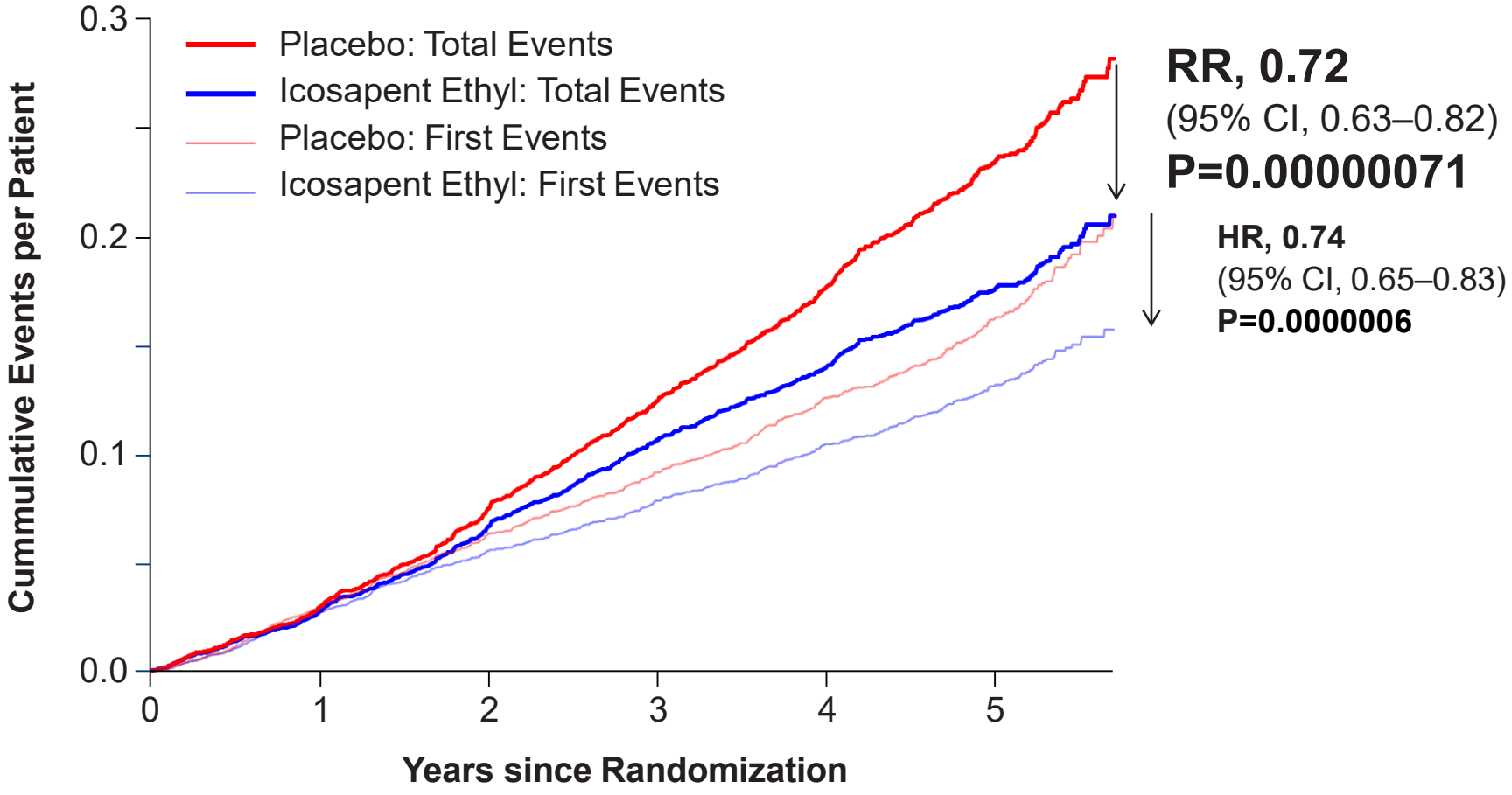
Key Secondary: CV Death, MI, Stroke

AMARIN

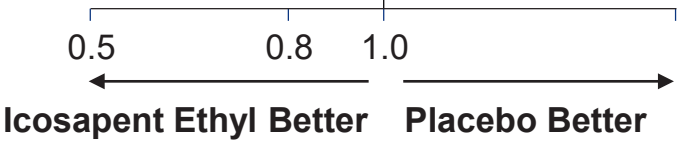
Key Secondary Composite Endpoint



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

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}



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

AMARIN

Endpoint/Model	Rate/Hazard Ratio (95% CI)	P-value
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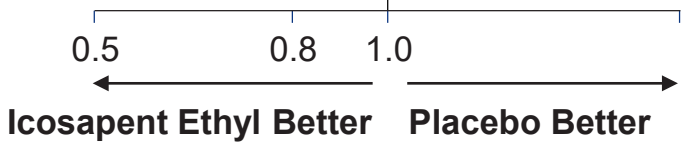
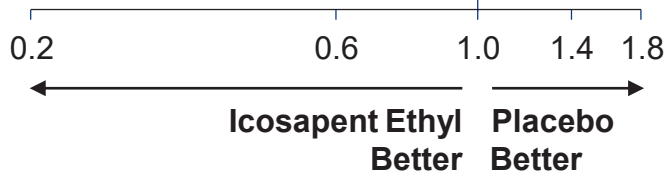
Second event	0.68 (0.60–0.78)	1.8×10^{-8}
Third event	0.69 (0.59–0.82)	2.0×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.72 (0.63–0.82)	7.1×10^{-7}
Modified WLW		
First event	0.74 (0.65–0.83)	7.0×10^{-7}
Second event	0.75 (0.63–0.89)	1.1×10^{-3}
Third event	0.79 (0.65–0.96)	0.017



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

Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

TIME TO FIRST EVENT – 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**

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 cost-effectiveness analyses now underway

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

Conclusions

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

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

Conclusions

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

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

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

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

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

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

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

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

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

Conclusions

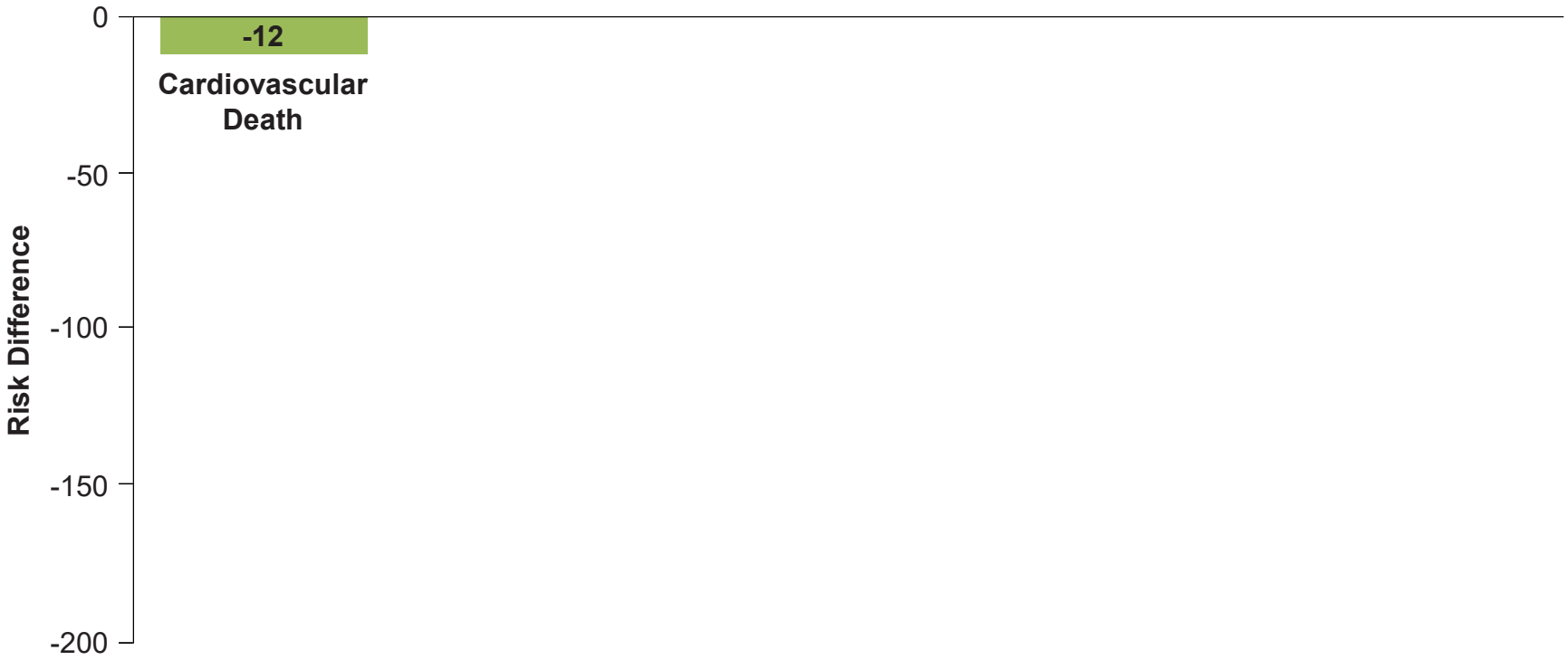
Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **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

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

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



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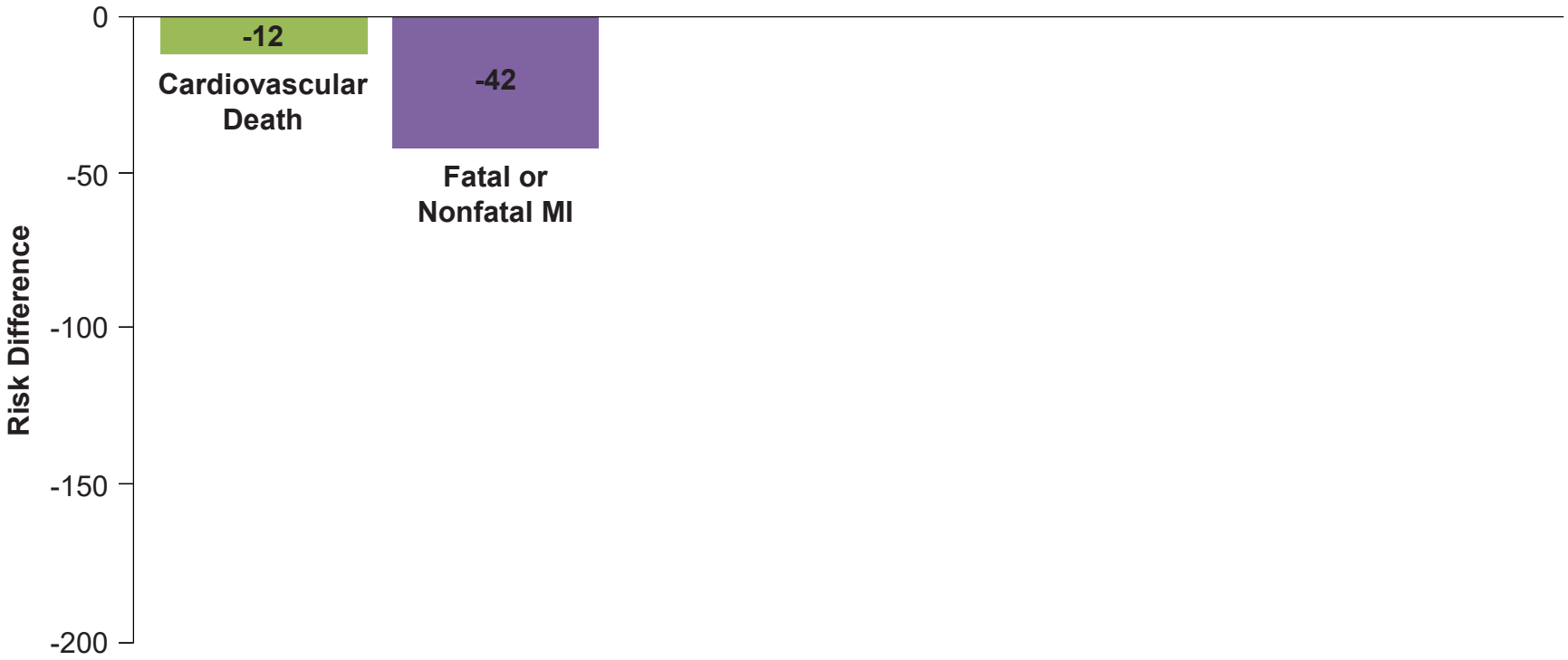

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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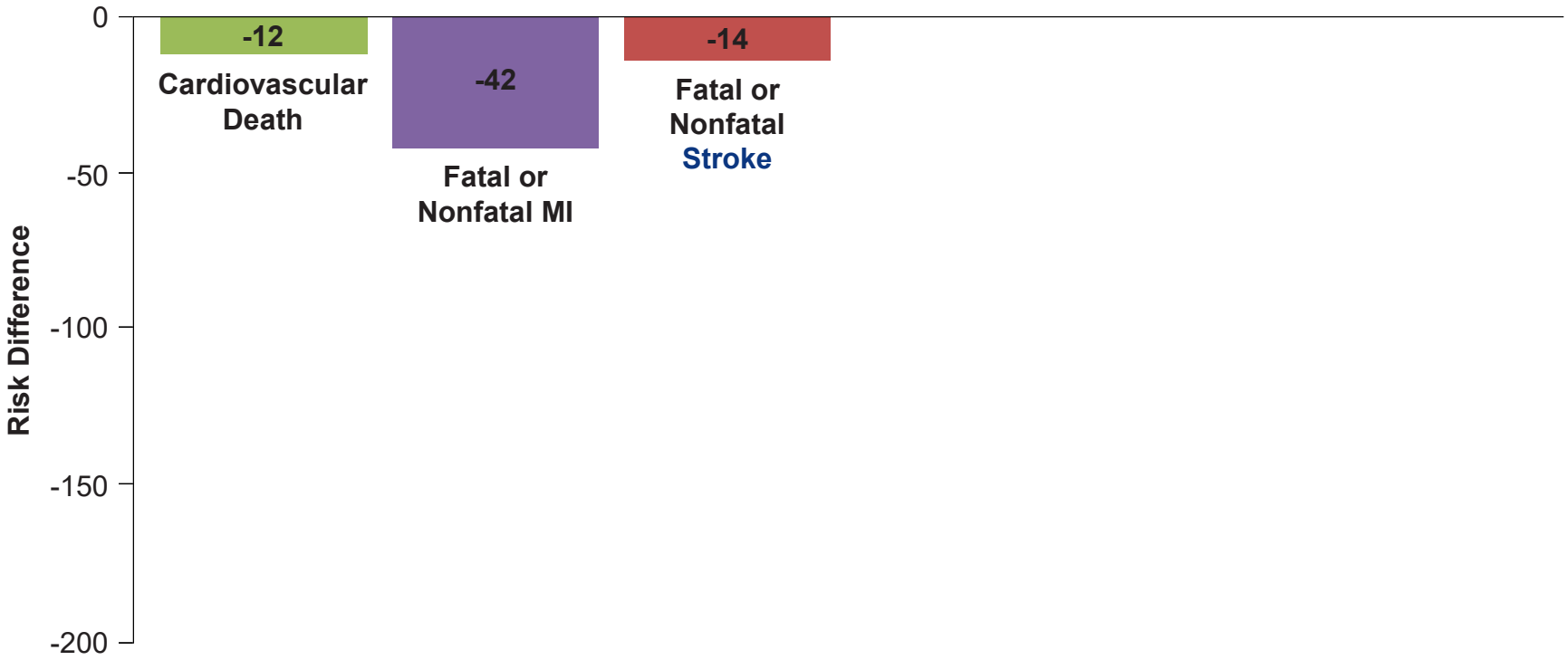
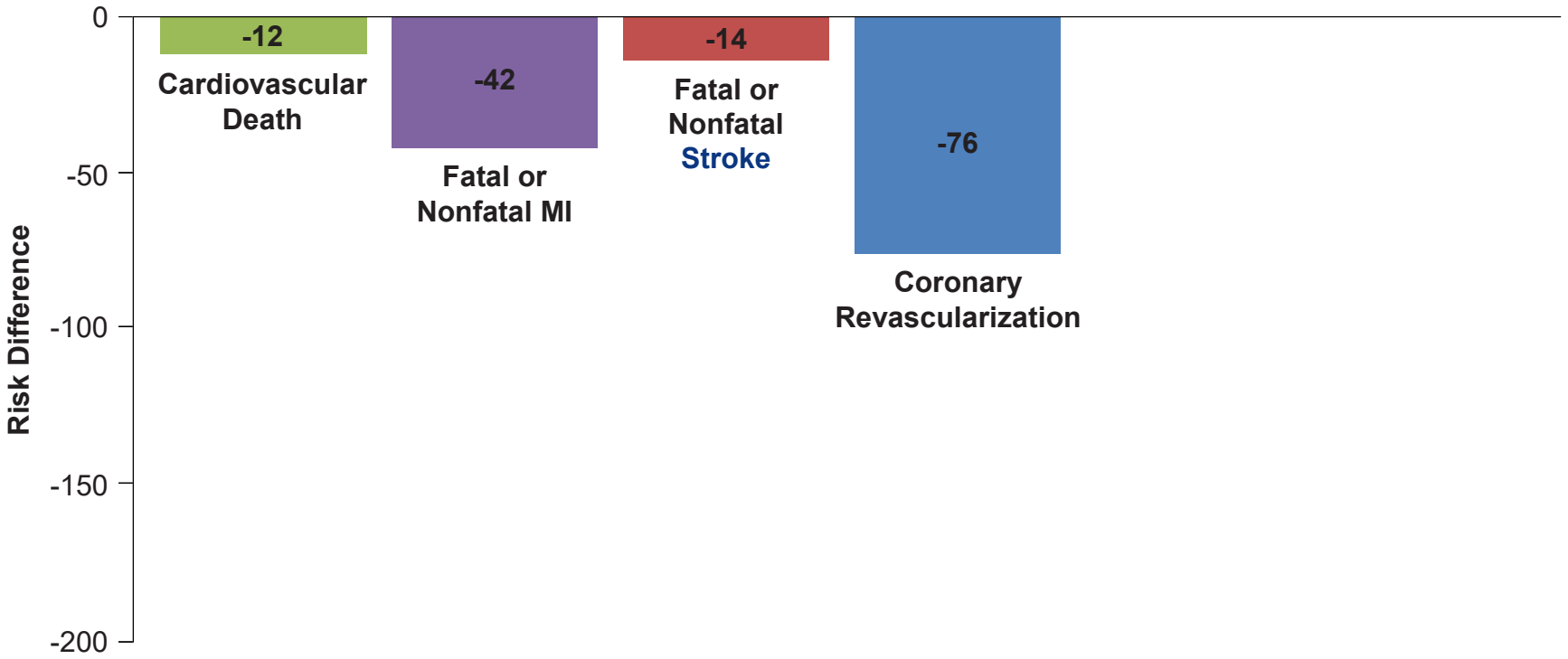


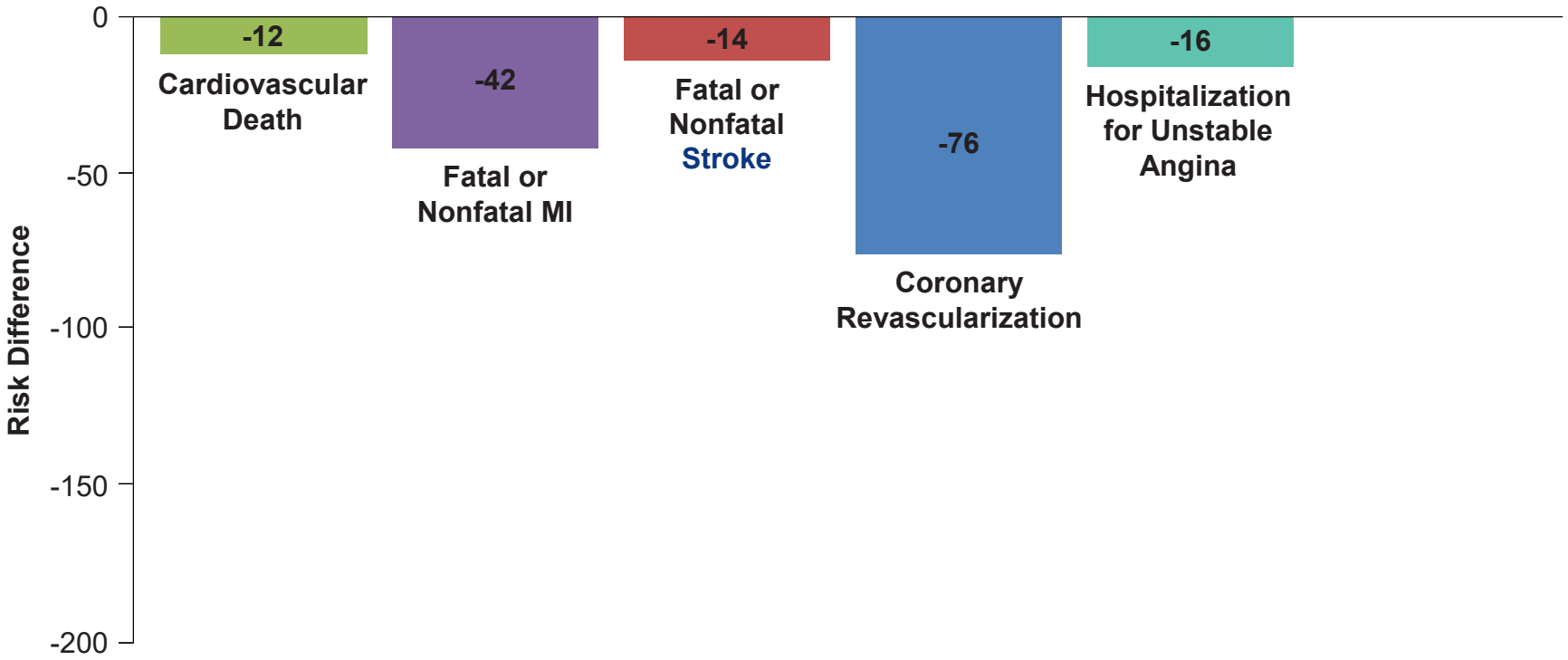
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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



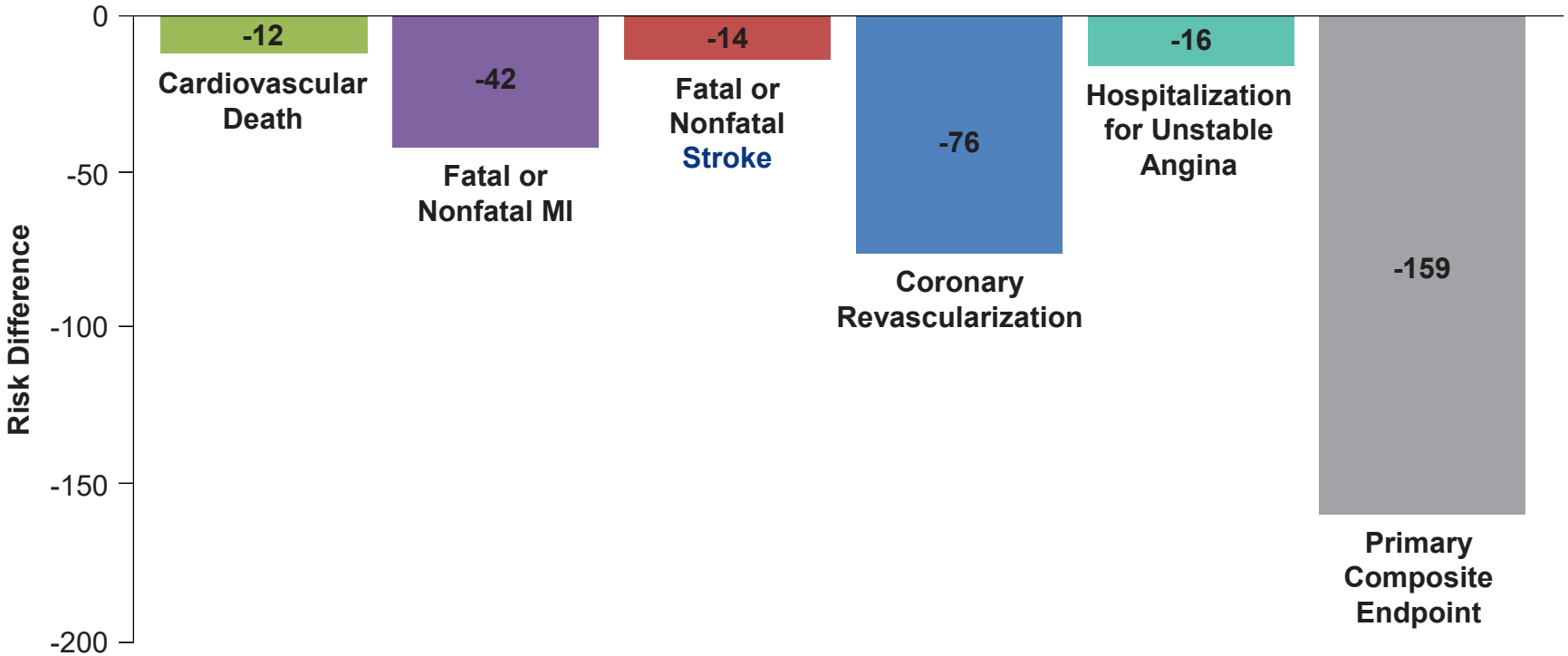
Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019.

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



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

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



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

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

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JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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

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BACK-UPS

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.

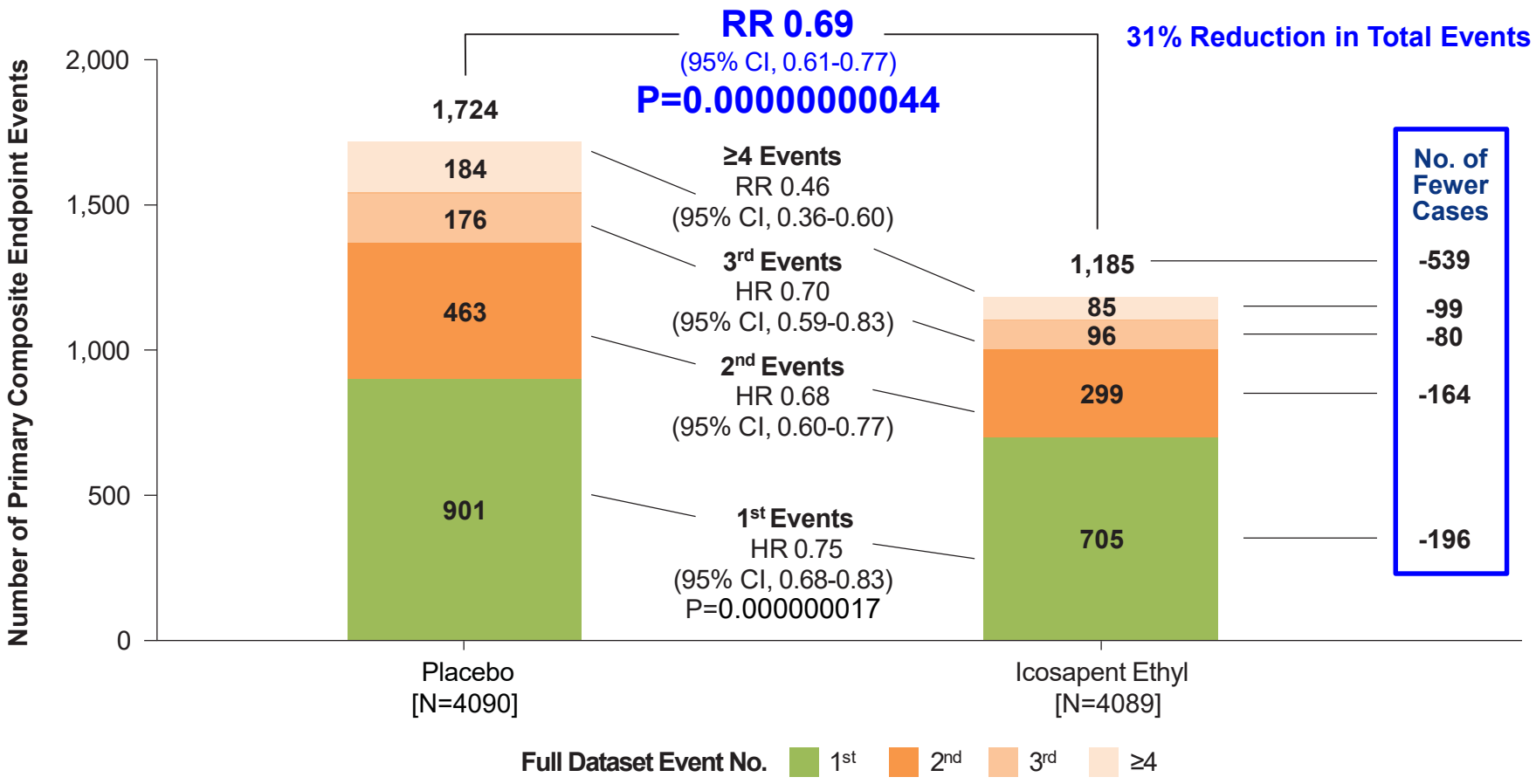
TGs were also measured from blood drawn at the randomization visit, but randomization values were not utilized for study qualification. Randomization values did not always fall within the inclusion criteria that were previously met at a qualifying visit.

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).

Bhatt DL. ACC 2019, New Orleans.

Distribution of First and Subsequent Events

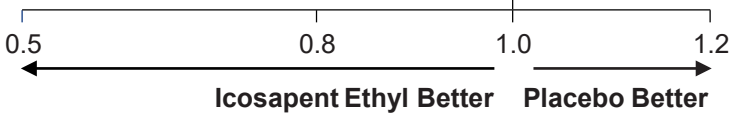


Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

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, Unadjusted)

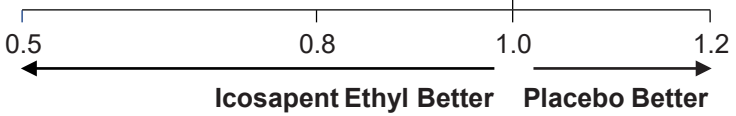
Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint		
Negative binomial	0.68 (0.61, 0.77)	1.5×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.5×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	9.1×10^{-11}
Modified WLW		
First event	0.76 (0.69, 0.83)	2.7×10^{-8}
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



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)

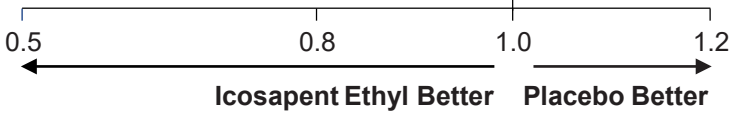
Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Primary Composite Endpoint		
Negative binomial	0.70 (0.62, 0.78)	3.6×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.3×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	5.2×10^{-11}
Modified WLW		
First event	0.75 (0.68, 0.83)	1.6×10^{-8}
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



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)

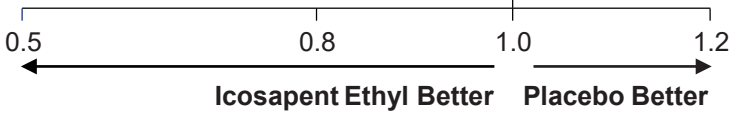
Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint		
Negative binomial	0.68 (0.61, 0.77)	1.5×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.5×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	9.1×10^{-11}
Modified WLW		
First event	0.76 (0.69, 0.83)	2.7×10^{-8}
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



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

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

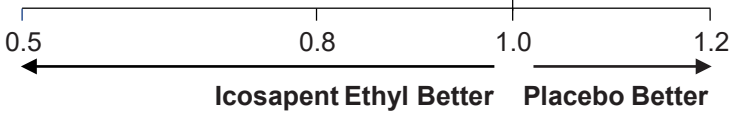
Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.82)	8.9×10^{-7}
Andersen-Gill (I)	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)	0.72 (0.63, 0.82)	1.2×10^{-6}
Modified WLW		
First event	0.74 (0.65, 0.83)	7.4×10^{-7}
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



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, Adjusted)

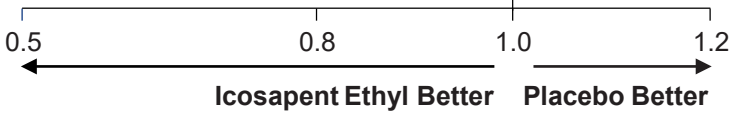
Endpoint/Model	Adjusted Rate/Hazard Ratio (95% CI)	Adjusted P-value
Primary Composite Endpoint		
Negative binomial	0.70 (0.62, 0.78)	3.6×10^{-10}
Andersen-Gill (I)	0.69 (0.64, 0.74)	3.3×10^{-21}
Andersen-Gill (II)	0.69 (0.61, 0.77)	5.2×10^{-11}
Modified WLW		
First event	0.75 (0.68, 0.83)	1.6×10^{-8}
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



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

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



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 (Full Dataset, Unadjusted)

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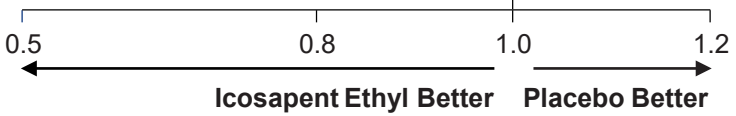
Endpoint/Model	Unadjusted Rate/Hazard Ratio (95% CI)	Unadjusted P-value
Primary Composite Endpoint		
Negative binomial	0.67 (0.60, 0.76)	1.6×10^{-10}
Andersen-Gill (I)	0.68 (0.63, 0.74)	3.4×10^{-22}
Andersen-Gill (II)	0.68 (0.61, 0.77)	4.5×10^{-11}
Modified WLW		
First event	0.76 (0.69, 0.83)	2.7×10^{-8}
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



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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
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Negative binomial	0.69 (0.61, 0.77)	4.4×10^{-10}
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Andersen-Gill (II)	0.68 (0.61, 0.76)	3.4×10^{-11}
Modified WLW		
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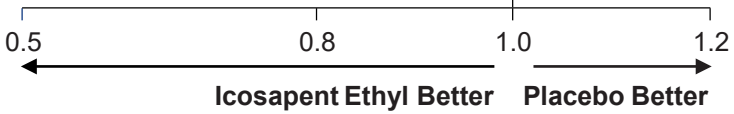
Second event	0.68 (0.60, 0.78)	3.1×10^{-9}
Third event	0.70 (0.60, 0.83)	2.1×10^{-5}
Key Secondary Composite Endpoint		
Negative binomial	0.71 (0.62, 0.82)	1.2×10^{-6}
Andersen-Gill (I)	0.71 (0.63, 0.79)	1.7×10^{-10}
Andersen-Gill (II)	0.71 (0.62, 0.81)	3.4×10^{-7}
Modified WLW		
First event	0.74 (0.65, 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



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

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

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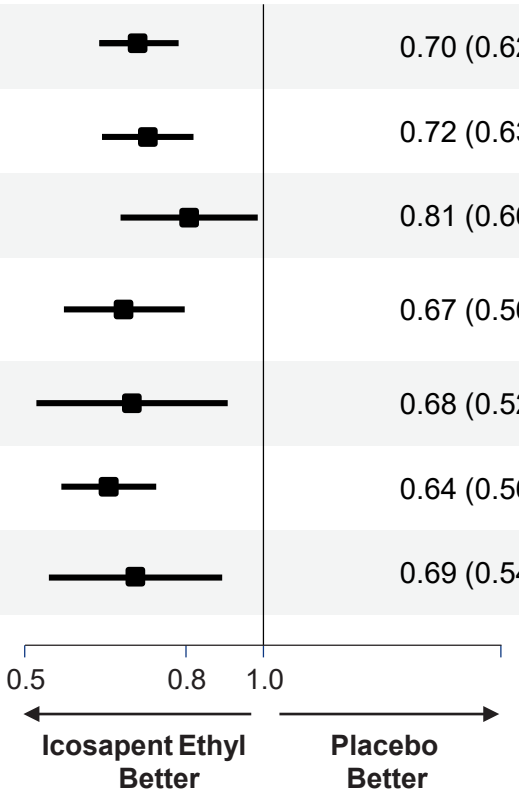
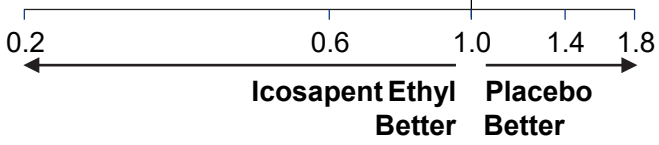
Endpoint	Icosapent Ethyl rate per 1000 patient years	Placebo rate per 1000 patient years	Rate Ratio (95% CI)	P-value
Primary composite endpoint	61	89	0.70 (0.62–0.78)	3.6×10^{-10}
Key secondary composite endpoint	32	44	0.72 (0.63–0.82)	7.1×10^{-7}
Cardiovascular death	10	12	0.81 (0.66–0.99)	0.0362
Fatal 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



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

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**

Bhatt DL. ACC 2019, New Orleans.

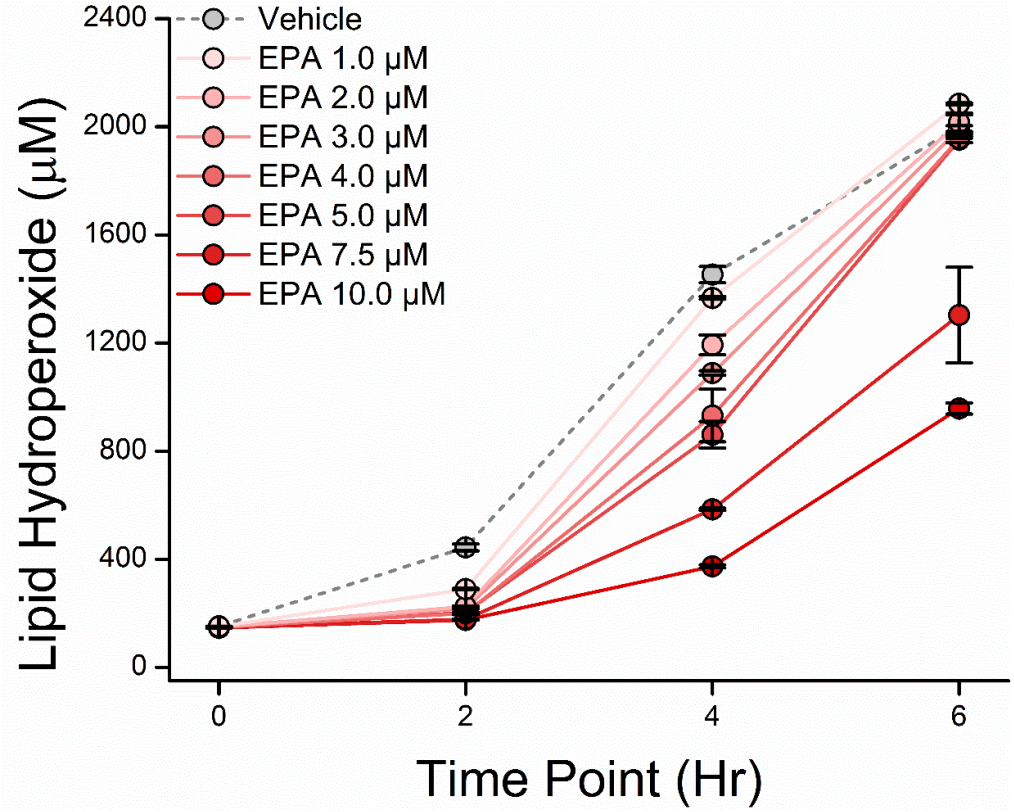
Mechanistic Data Presented at ACC

Research regarding the mechanism of action of EPA is ongoing

- *EPA Inhibits Membrane Lipid Oxidation in a Concentration-dependent Manner at Pharmacologic Doses In Vitro,* another study presented at ACC measured the effects of EPA on membrane lipid oxidation.
- EPA significantly inhibited lipid hydroperoxide (LOOH) formation, a measure of lipid oxidation, in a concentration-dependent manner.
- After 4 hours, EPA inhibited LOOH by 6% at an EPA concentration of 1.0 µM, increasing to 74% inhibition at the maximum concentration

Sherratt SCR, Mason RP. ACC 2019, New Orleans.

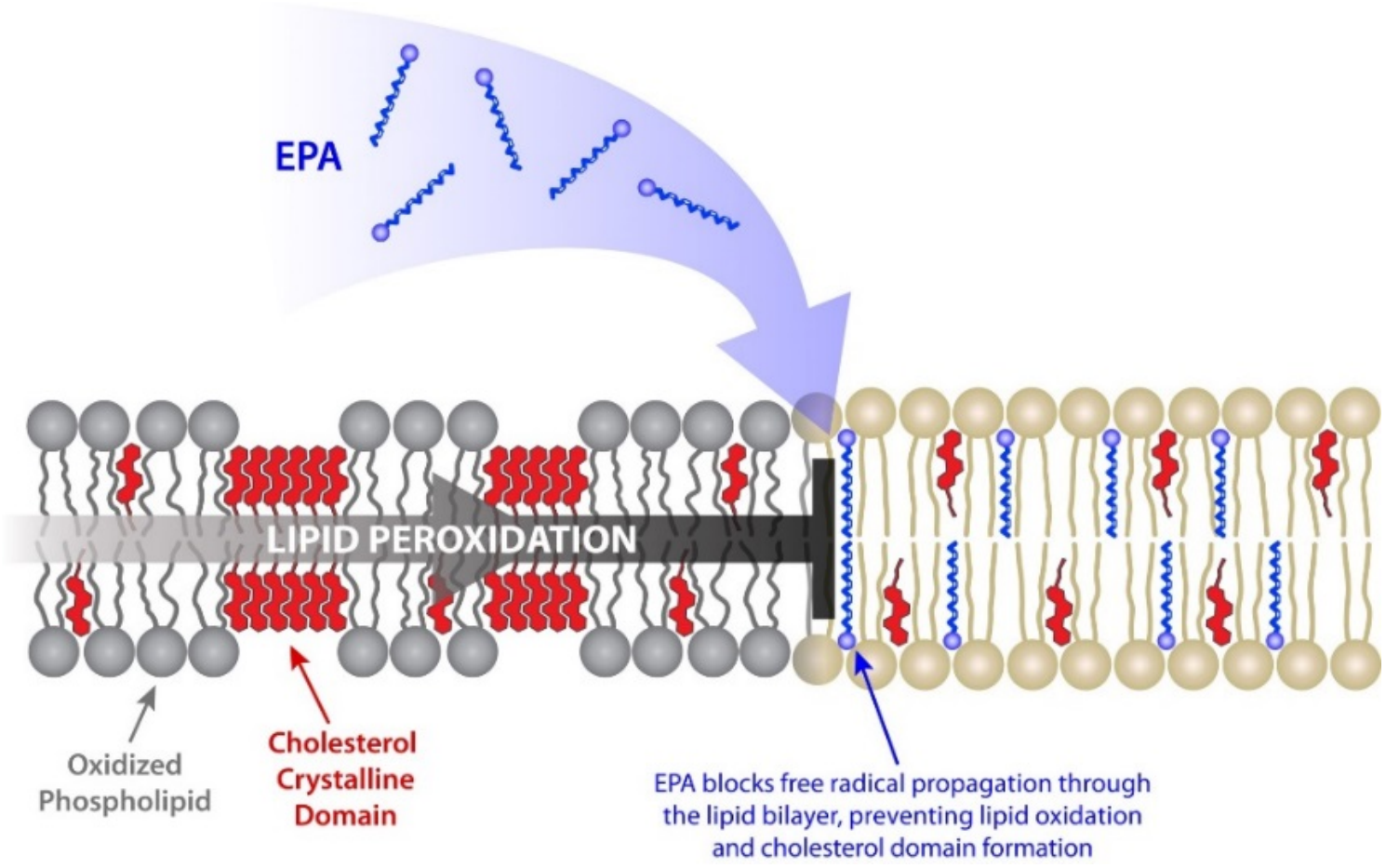
Concentration-dependent effects of EPA on inhibition of lipid peroxidation in model membranes through 6 hours.



Results shown as mean ± SD (N = 3).

Interpretation

Schematic illustration of mechanism of free radical scavenging by EPA in the membrane.



What Does EPA Membrane Oxidation Inhibition Mean?

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Summary:

- These data support a concentration-dependent antioxidant effect for EPA in a pure formulation at pharmacologic concentrations
- As membrane lipid oxidation is an important contributor to atherosclerosis, the inhibition of oxidation by EPA at an appropriate high dose and concentration provide a potential mechanism for reduced cardiovascular risk

Potential Atheroprotective Benefits of EPA

Schematic illustration of atheroprotective benefits of EPA and its membrane stabilization effects.