Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

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on Behalf of the **REDUCE-IT** Investigators

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno, 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), Medtelligence/ReachMD (CME steering committees), 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, Afimmune, **Amarin**, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Fractyl, 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, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.

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

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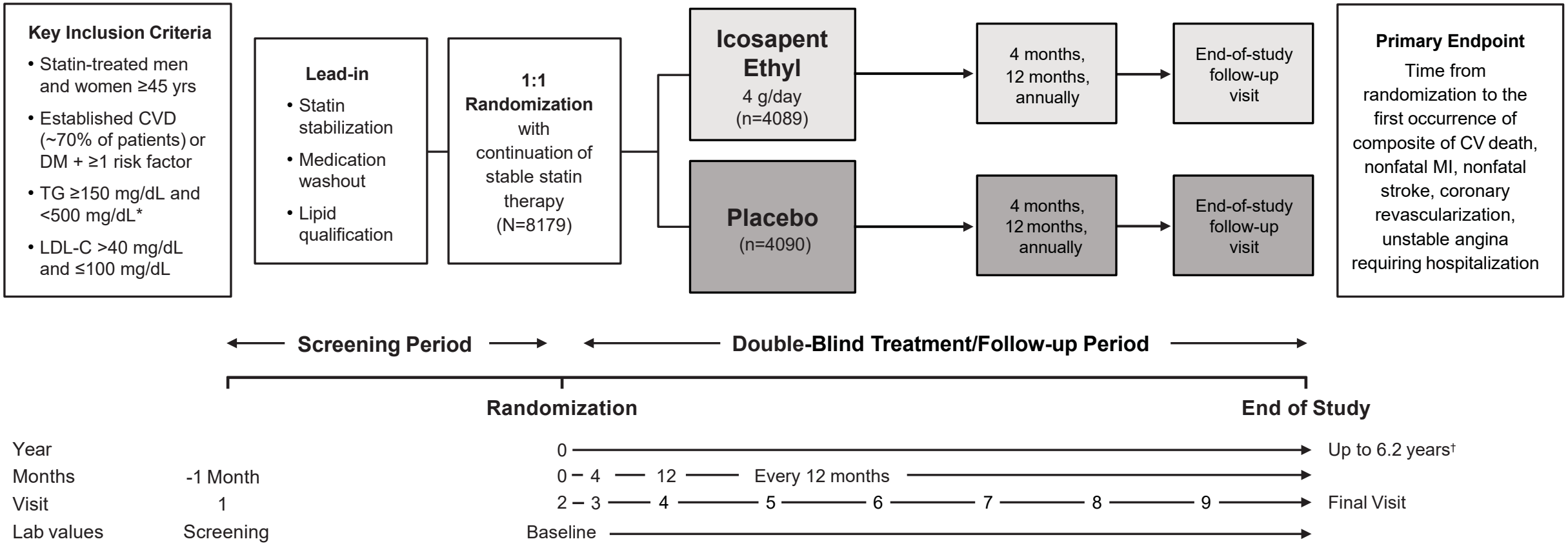
All analyses independently validated by Baim Clinical Research Institute.

REDUCE-IT Design



*Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

†Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Adapted with permission‡ from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol.* 2017;40:138-148. REDUCE-IT ClinicalTrials.gov number, NCT01492361.
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Primary and Key Secondary Composite Endpoints

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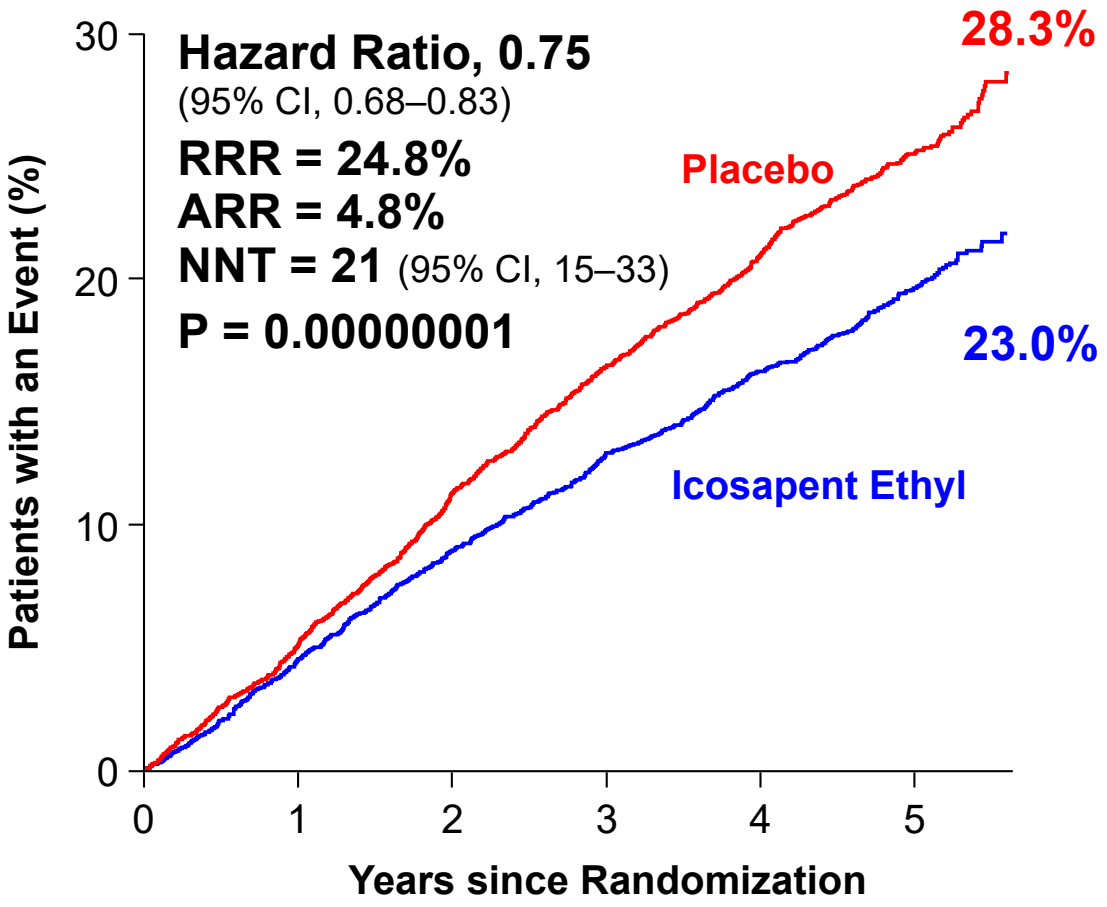
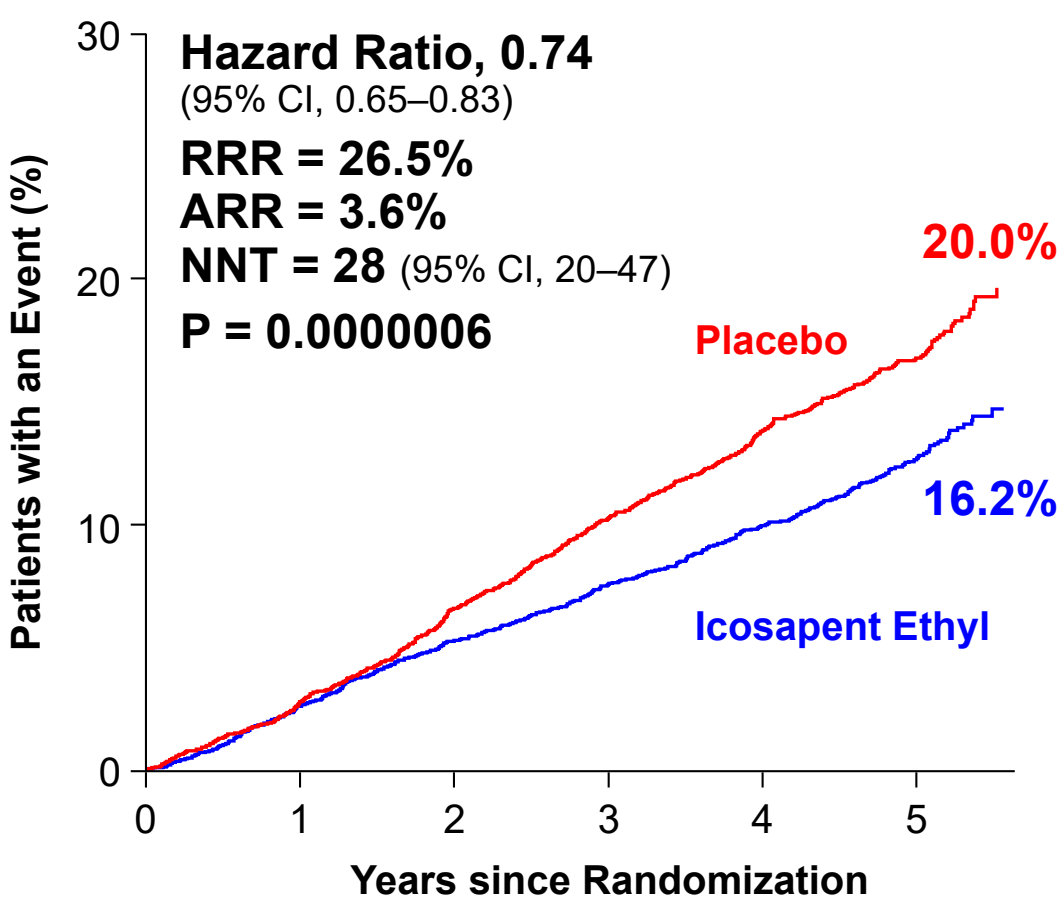
Primary Composite Endpoint:

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



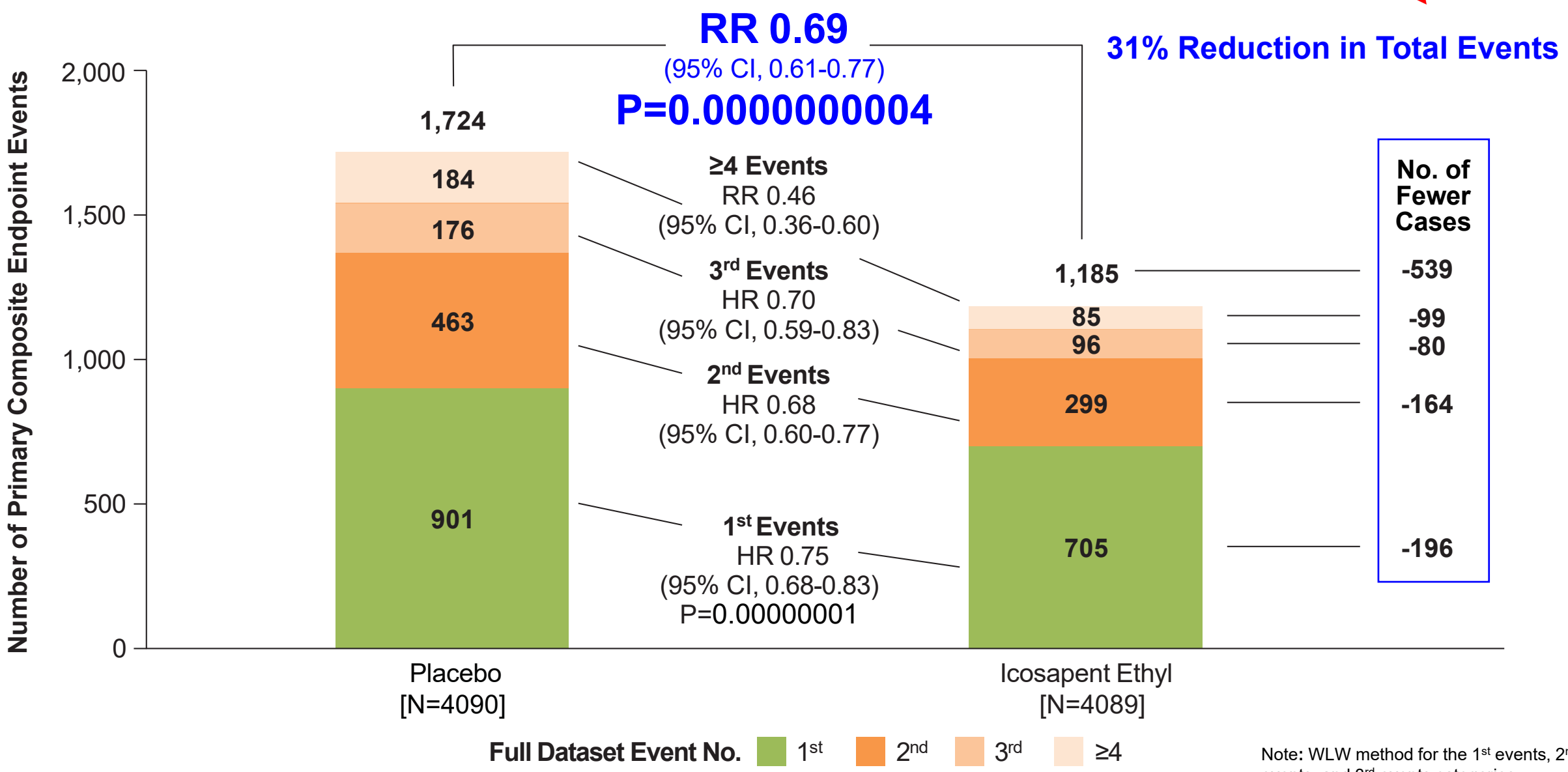
Key Secondary Composite Endpoint:

CV Death, MI, Stroke



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago.

First and Subsequent Events – Full Data



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;73:2791-2802. Bhatt DL. ACC 2019, New Orleans.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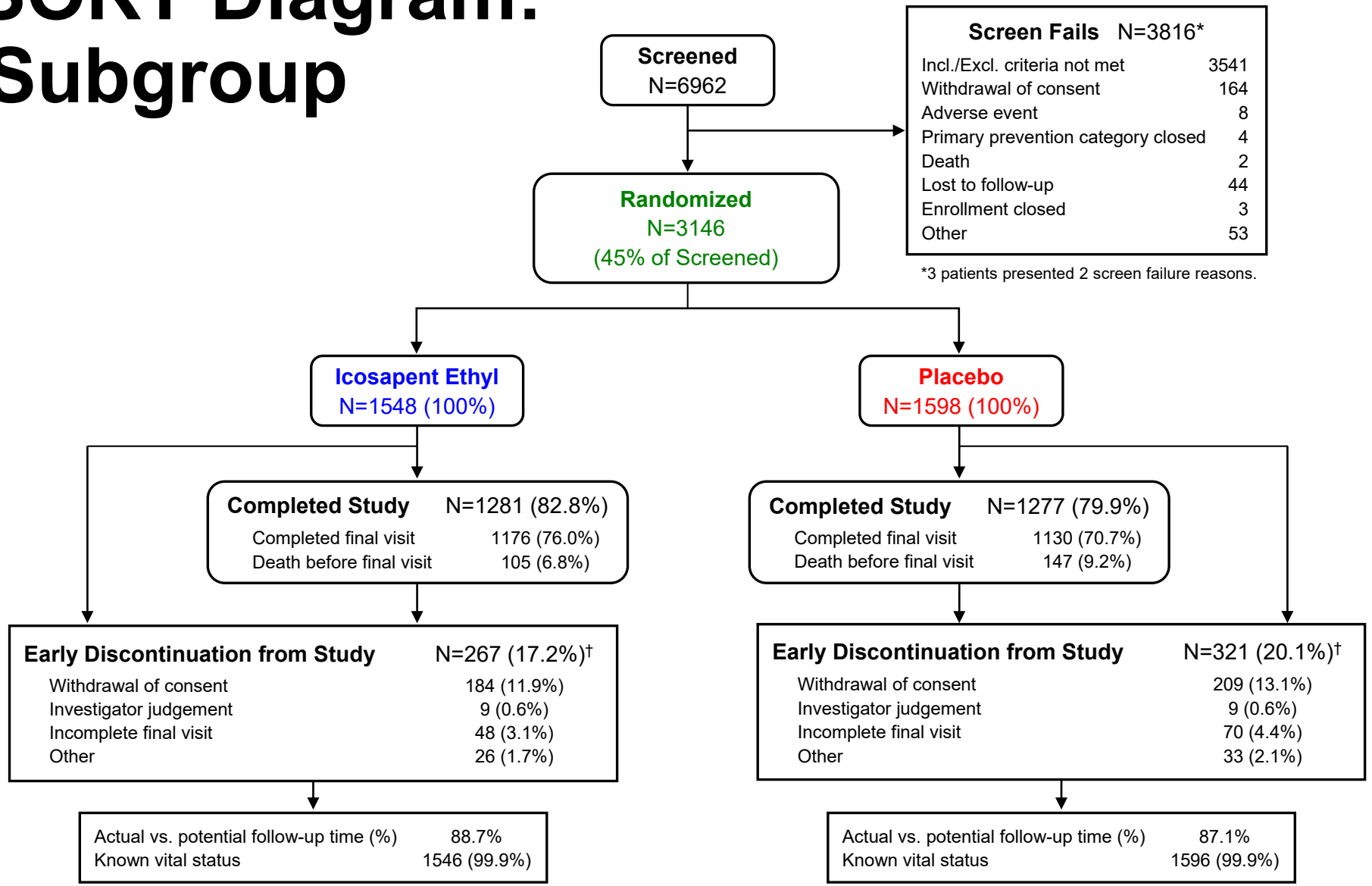
USA

CONSORT Diagram: USA Subgroup

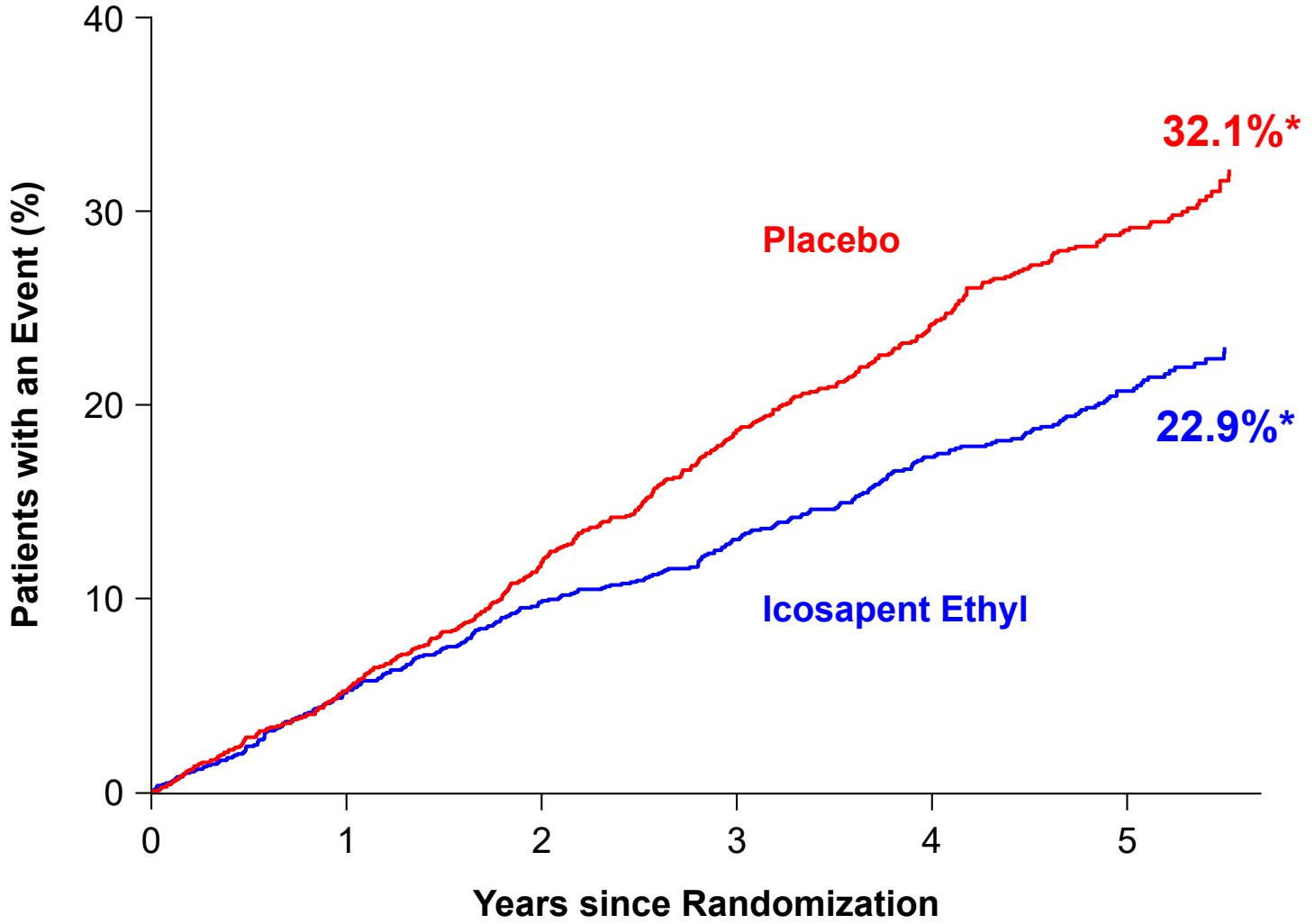


†Early discontinuation from study (17.2% icosapent ethyl; 20.1% placebo) includes patients who discontinued after having a primary event (15 [1.0%] icosapent ethyl; 34 [2.1%] placebo) and prior to having an event (252 [16.3%] icosapent ethyl; 287 [18.0%] placebo).

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. DOI: 10.1161/CIRCULATIONAHA.119.044440.

Primary End Point: USA Subgroup

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



Hazard Ratio, 0.69
(95% CI, 0.59–0.80)

RRR = 31%

ARR = 6.5%

NNT = 15 (95% CI, 11–27)

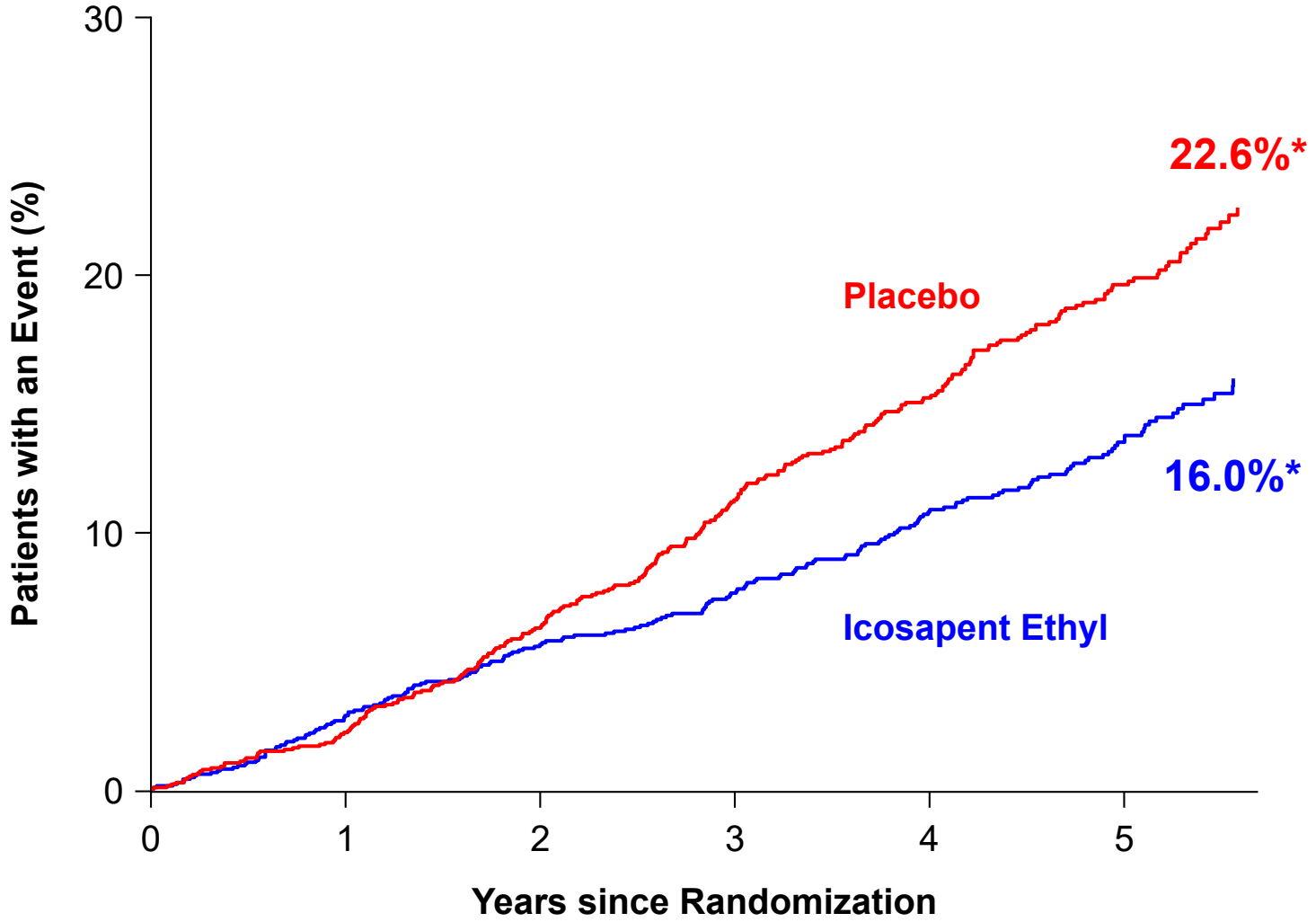
P = 0.000001

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. Bhatt DL. AHA 2019, Philadelphia.

Key Secondary End Point: USA Subgroup

CV Death, MI, Stroke



Hazard Ratio, 0.69
(95% CI, 0.57–0.83)

RRR = 31%

ARR = 4.6%

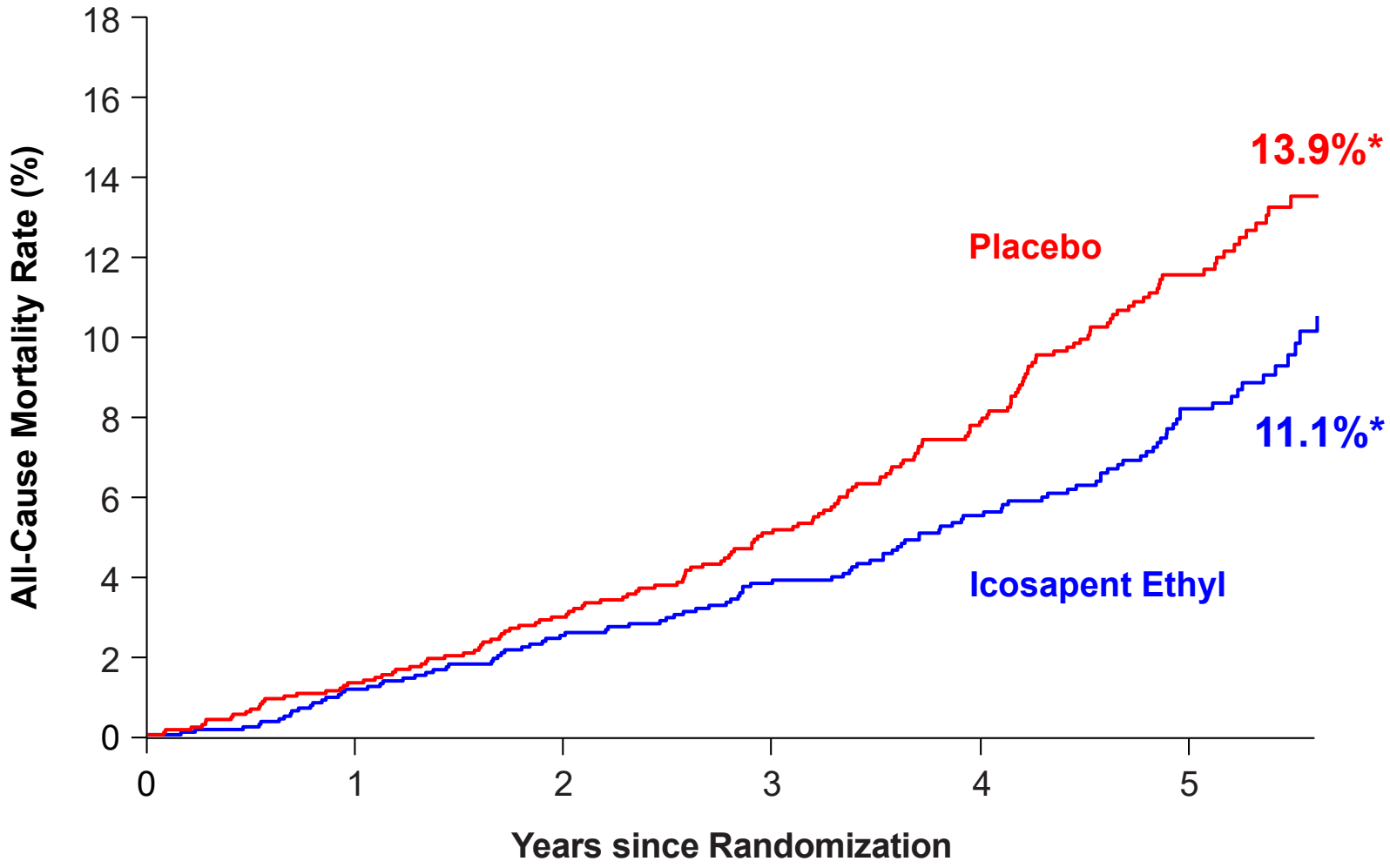
NNT = 22 (95% CI, 14–47)

P = 0.00008

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. Bhatt DL. AHA 2019, Philadelphia.

All-Cause Mortality: USA Subgroup



Hazard Ratio, 0.70
(95% CI, 0.55–0.90)

RRR = 30%

ARR = 2.6%

NNT = 39 (95% CI, 22–154)

P = 0.004

$P_{interaction}$ = 0.02

*Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

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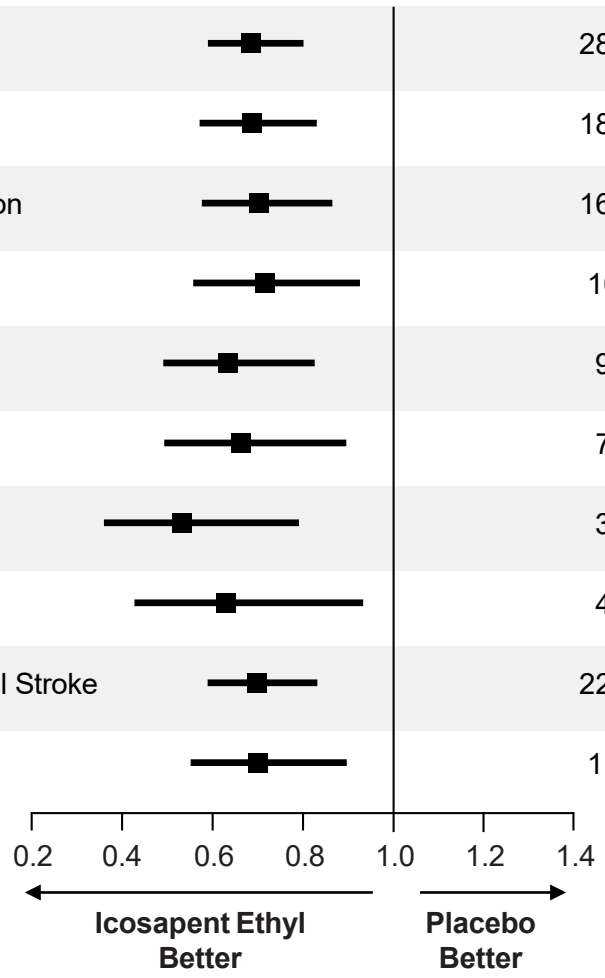
Prespecified Hierarchical Testing: USA Subgroup

Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	RRR	P-value
Primary Composite (ITT)	281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	31%▼	0.000001
Key Secondary Composite (ITT)	187/1548 (12.1%)	266/1598 (16.6%)	0.69 (0.57–0.83)	31%▼	0.00008
Cardiovascular Death or Nonfatal Myocardial Infarction	160/1548 (10.3%)	222/1598 (13.9%)	0.71 (0.58–0.86)	29%▼	0.0007
Fatal or Nonfatal Myocardial Infarction	103/1548 (6.7%)	141/1598 (8.8%)	0.72 (0.56–0.93)	28%▼	0.01
Urgent or Emergency Revascularization	94/1548 (6.1%)	144/1598 (9.0%)	0.64 (0.49–0.83)	36%▼	0.0006
Cardiovascular Death	72/1548 (4.7%)	107/1598 (6.7%)	0.66 (0.49–0.90)	34%▼	0.007
Hospitalization for Unstable Angina	38/1548 (2.5%)	71/1598 (4.4%)	0.53 (0.36–0.79)	47%▼	0.002
Fatal or Nonfatal Stroke	41/1548 (2.6%)	65/1598 (4.1%)	0.63 (0.43–0.93)	37%▼	0.02
Total Mortality/Nonfatal Myocardial Infarction/Nonfatal Stroke	221/1548 (14.3%)	309/1598 (19.3%)	0.70 (0.59–0.83)	30%▼	0.00005
Total Mortality	111/1548 (7.2%)	156/1598 (9.8%)	0.70 (0.55–0.90)	30%▼	0.004

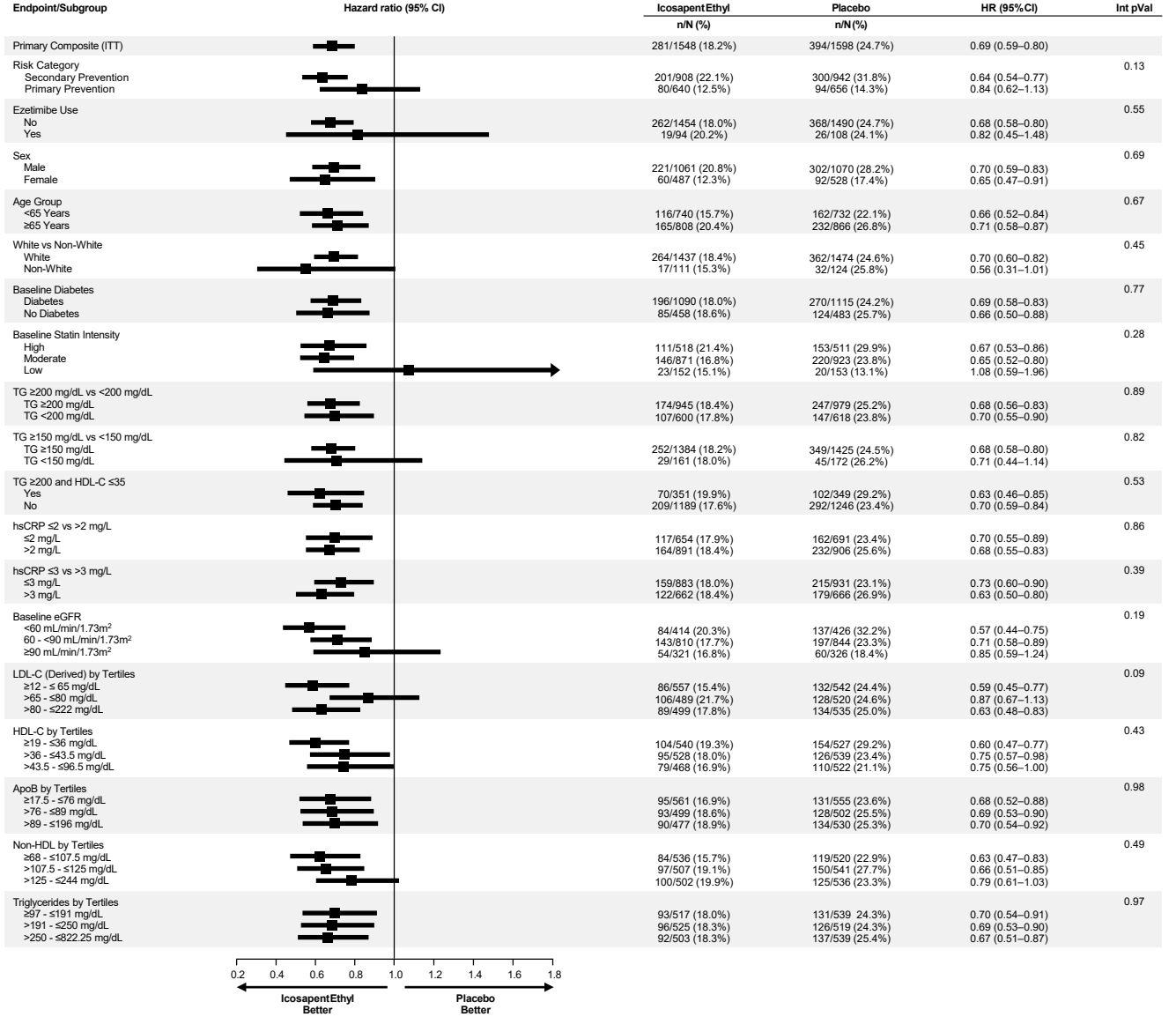


Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. Bhatt DL. AHA 2019, Philadelphia.

RRR denotes relative risk reduction

Primary Endpoint: USA Subgroup

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

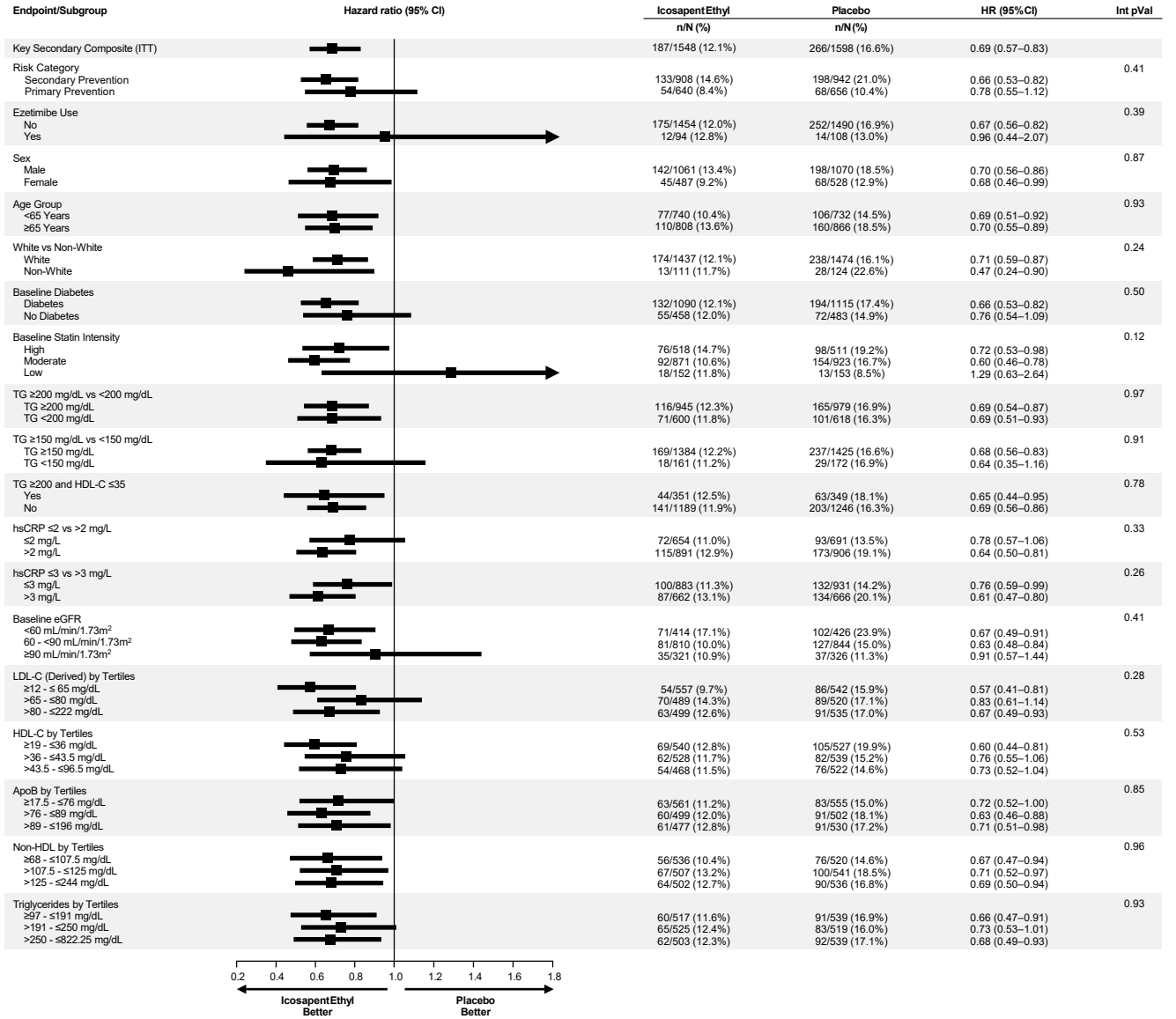


Endpoint/Subgroup	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int pVal
Primary Composite (ITT)	281/1548 (18.2%)	394/1598 (24.7%)	0.69 (0.59–0.80)	
Risk Category				0.13
Secondary Prevention	201/908 (22.1%)	300/942 (31.8%)	0.64 (0.54–0.77)	
Primary Prevention	80/640 (12.5%)	94/656 (14.3%)	0.84 (0.62–1.13)	
Ezetimibe Use				0.55
No	262/1454 (18.0%)	368/1490 (24.7%)	0.68 (0.58–0.80)	
Yes	19/94 (20.2%)	26/108 (24.1%)	0.82 (0.45–1.48)	
Sex				0.69
Male	221/1061 (20.8%)	302/1070 (28.2%)	0.70 (0.59–0.83)	
Female	60/487 (12.3%)	92/528 (17.4%)	0.65 (0.47–0.91)	
Age Group				0.67
<65 Years	116/740 (15.7%)	162/732 (22.1%)	0.66 (0.52–0.84)	
≥65 Years	165/808 (20.4%)	232/866 (26.8%)	0.71 (0.58–0.87)	
White vs Non-White				0.45
White	264/1437 (18.4%)	362/1474 (24.6%)	0.70 (0.60–0.82)	
Non-White	17/111 (15.3%)	32/124 (25.8%)	0.56 (0.31–1.01)	
Baseline Diabetes				0.77
Diabetes	196/1090 (18.0%)	270/1115 (24.2%)	0.69 (0.58–0.83)	
No Diabetes	85/458 (18.6%)	124/483 (25.7%)	0.66 (0.50–0.88)	
Baseline Statin Intensity				0.28
High	111/518 (21.4%)	153/511 (29.9%)	0.67 (0.53–0.86)	
Moderate	146/871 (16.8%)	220/923 (23.8%)	0.65 (0.52–0.80)	
Low	23/152 (15.1%)	20/153 (13.1%)	1.08 (0.59–1.96)	
TG ≥200 mg/dL vs <200 mg/dL				0.89
TG ≥200 mg/dL	174/945 (18.4%)	247/979 (25.2%)	0.68 (0.56–0.83)	
TG <200 mg/dL	107/600 (17.8%)	147/618 (23.8%)	0.70 (0.55–0.90)	
TG ≥150 mg/dL vs <150 mg/dL				0.82
TG ≥150 mg/dL	252/1384 (18.2%)	349/1425 (24.5%)	0.68 (0.58–0.80)	
TG <150 mg/dL	29/161 (18.0%)	45/172 (26.2%)	0.71 (0.44–1.14)	
TG ≥200 and HDL-C ≤35				0.53
Yes	70/351 (19.9%)	102/349 (29.2%)	0.63 (0.46–0.85)	
No	209/1189 (17.6%)	292/1246 (23.4%)	0.70 (0.59–0.84)	
hsCRP ≤2 vs >2 mg/L				0.86
≤2 mg/L	117/654 (17.9%)	162/691 (23.4%)	0.70 (0.55–0.89)	
>2 mg/L	164/891 (18.4%)	232/906 (25.6%)	0.68 (0.55–0.83)	
hsCRP ≤3 vs >3 mg/L				0.39
≤3 mg/L	159/883 (18.0%)	215/931 (23.1%)	0.73 (0.60–0.90)	
>3 mg/L	122/662 (18.4%)	179/666 (26.9%)	0.63 (0.50–0.80)	
Baseline eGFR				0.19
<60 mL/min/1.73m^2	84/414 (20.3%)	137/426 (32.2%)	0.57 (0.44–0.75)	
60 - <90 mL/min/1.73m^2	143/810 (17.7%)	197/844 (23.3%)	0.71 (0.58–0.89)	
≥90 mL/min/1.73m^2	54/321 (16.8%)	60/326 (18.4%)	0.85 (0.59–1.24)	
LDL-C (Derived) by Tertiles				0.09
≥12 - ≤ 65 mg/dL	86/557 (15.4%)	132/542 (24.4%)	0.59 (0.45–0.77)	
>65 - ≤80 mg/dL	106/489 (21.7%)	128/520 (24.6%)	0.87 (0.67–1.13)	
>80 - ≤222 mg/dL	89/499 (17.8%)	134/535 (25.0%)	0.63 (0.48–0.83)	
HDL-C by Tertiles				0.43
≥19 - ≤36 mg/dL	104/540 (19.3%)	154/527 (29.2%)	0.60 (0.47–0.77)	
>36 - ≤43.5 mg/dL	95/528 (18.0%)	126/539 (23.4%)	0.75 (0.57–0.98)	
>43.5 - ≤96.5 mg/dL	79/468 (16.9%)	110/522 (21.1%)	0.75 (0.56–1.00)	
ApoB by Tertiles				0.98
≥17.5 - ≤76 mg/dL	95/561 (16.9%)	131/555 (23.6%)	0.68 (0.52–0.88)	
>76 - ≤89 mg/dL	93/499 (18.6%)	128/502 (25.5%)	0.69 (0.53–0.90)	
>89 - ≤196 mg/dL	90/477 (18.9%)	134/530 (25.3%)	0.70 (0.54–0.92)	
Non-HDL by Tertiles				0.49
≥68 - ≤107.5 mg/dL	84/536 (15.7%)	119/520 (22.9%)	0.63 (0.47–0.83)	
>107.5 - ≤125 mg/dL	97/507 (19.1%)	150/541 (27.7%)	0.66 (0.51–0.85)	
>125 - ≤244 mg/dL	100/502 (19.9%)	125/536 (23.3%)	0.79 (0.61–1.03)	
Triglycerides by Tertiles				0.97
≥97 - ≤191 mg/dL	93/517 (18.0%)	131/539 24.3%)	0.70 (0.54–0.91)	
>191 - ≤250 mg/dL	96/525 (18.3%)	126/519 (24.3%)	0.69 (0.53–0.90)	
>250 - ≤822.25 mg/dL	92/503 (18.3%)	137/539 (25.4%)	0.67 (0.51–0.87)	

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. Bhatt DL. AHA 2019, Philadelphia.

Key Secondary Endpoint: Subgroups – USA

CV Death, MI, Stroke



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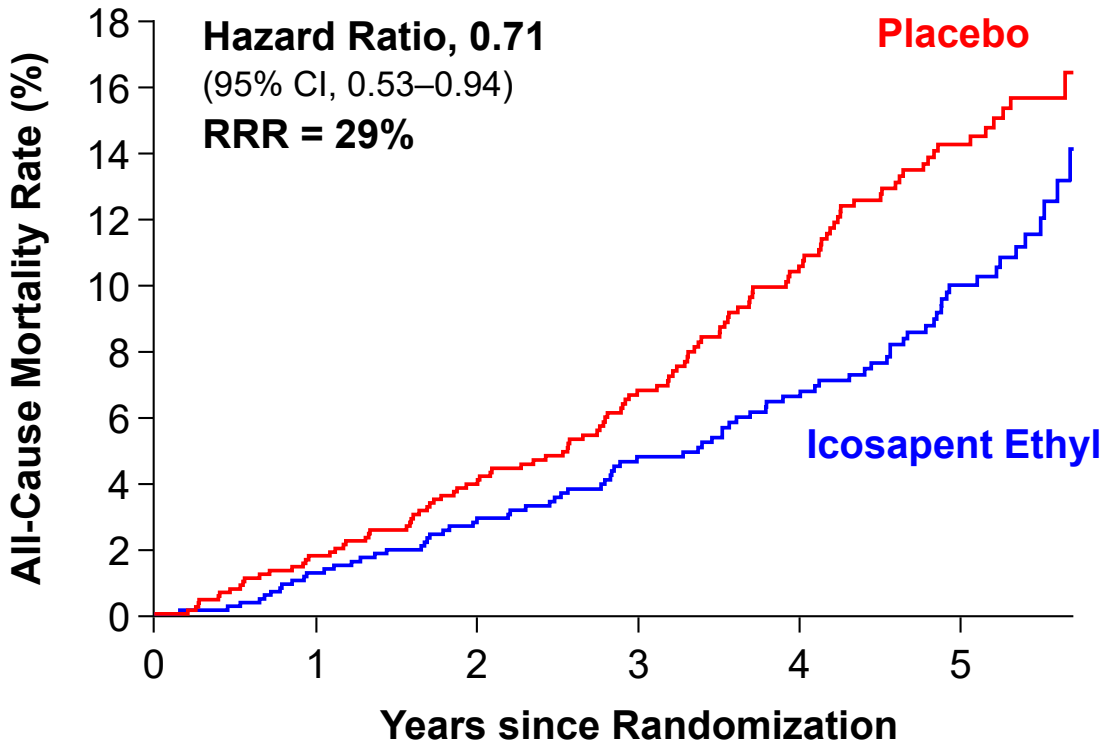
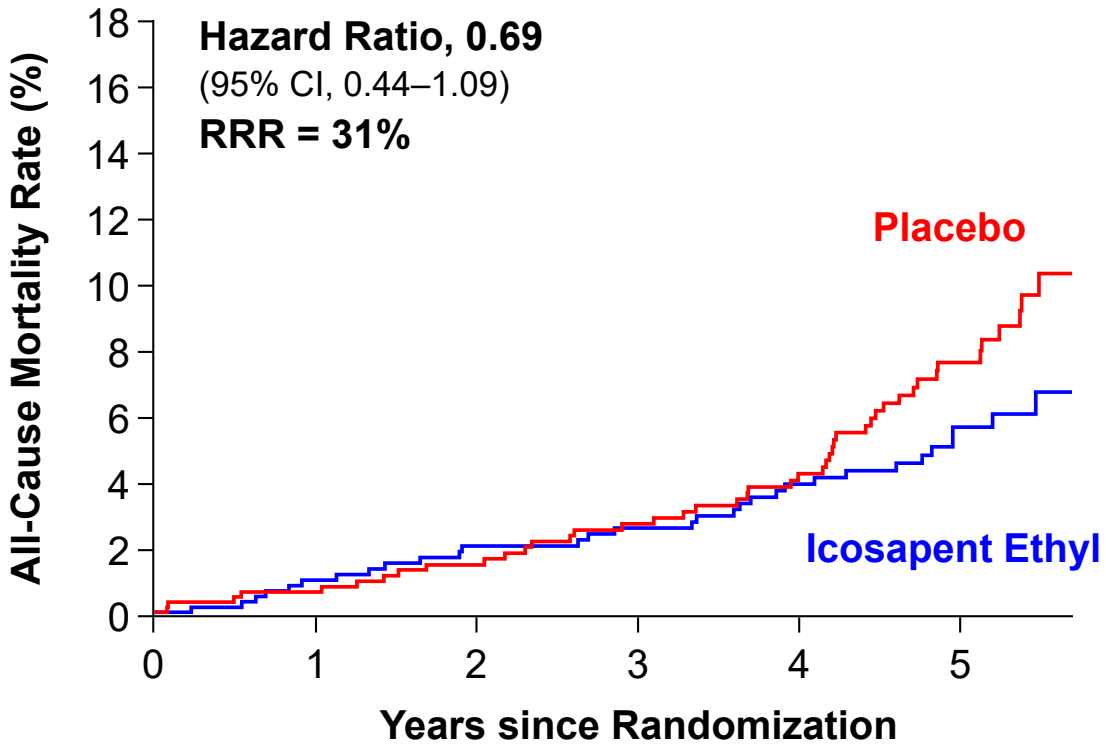
All-Cause Mortality: USA Subgroup by CV Risk Category

Secondary Prevention



Primary Prevention

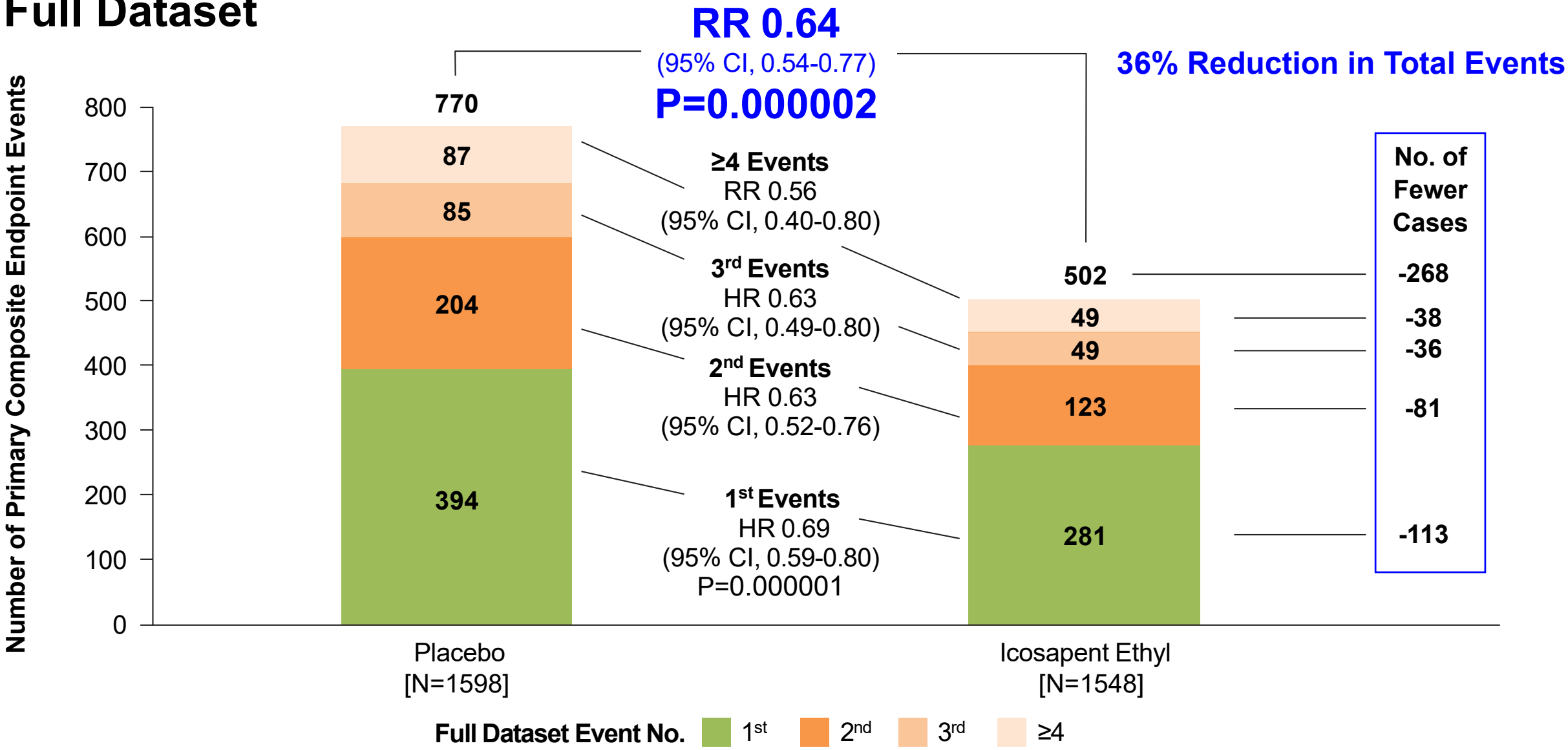


Note: The curves were visually truncated at 5.7 years because a limited number of events occurred beyond that time point; all patient data were included in the analyses.

Bhatt DL. AHA 2019, Philadelphia.

First and Subsequent Events: USA

Full Dataset



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

Safety Summary: USA Subgroup

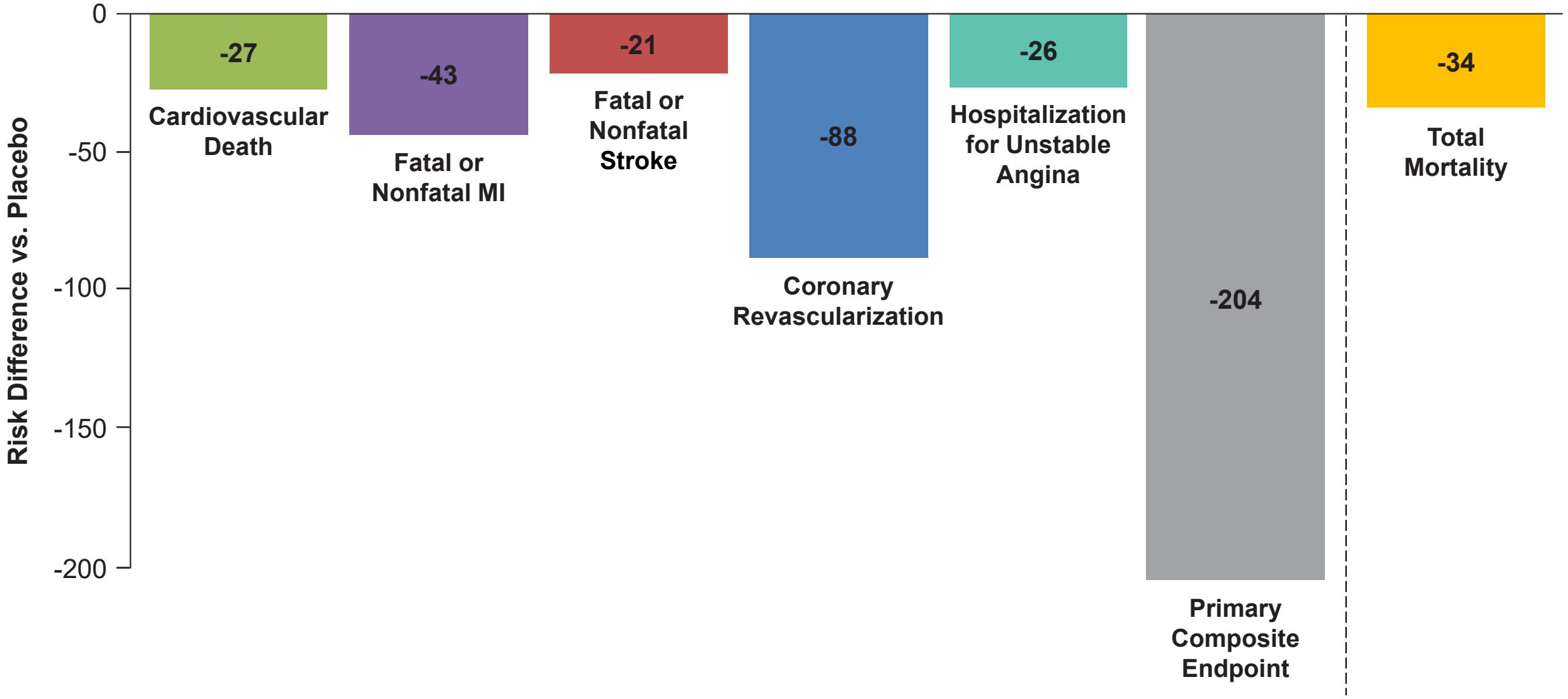
Treatment Emergent Adverse Events in the Safety Population

	Icosapent Ethyl (N=1548)	Placebo (N=1598)	P-value
Subjects with at Least One TEAE, n (%)	1354 (87.5)	1387 (86.8)	0.59
Severe TEAE	436 (28.2)	458 (28.7)	0.78
Drug-Related TEAE	188 (12.1)	183 (11.5)	0.58
Serious TEAE	533 (34.4)	571 (35.7)	0.46
Drug-Related Serious TEAE	5 (0.3)	2 (0.1)	0.28
TEAE Leading to Withdrawal of Study Drug	145 (9.4)	170 (10.6)	0.26
Drug-Related TEAE Leading to Withdrawal of Study Drug	56 (3.6)	75 (4.7)	0.15
Serious TEAE Leading to Withdrawal of Study Drug	31 (2.0)	48 (3.0)	0.09
Serious TEAE Leading to Death	36 (2.3)	53 (3.3)	0.11
Drug-Related Serious TEAE Leading to Withdrawal of Study Drug	1 (0.1)	2 (0.1)	>0.99

- Tolerability and safety findings were consistent with the full study population
- The tolerability and safety virtually identical to placebo; no significant differences in the overall rates of TEAEs or serious TEAEs
- A significant increase in minor bleeding (16.7% vs 13.6%, p=0.02), but no significant excess in serious adverse events related to bleeding
- There was a significant increase in the overall TEAE rate of atrial fibrillation or flutter (6.6% vs 4.5%, p=0.012), but not in either the category of serious adverse events of atrial fibrillation or flutter, or the adjudicated endpoint of hospitalization ≥24 hours for atrial fibrillation or flutter

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. Bhatt DL. AHA 2019, Philadelphia.

For Every 1000 Patients in the USA Treated with Icosapent Ethyl 4g/day for 5 Years



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Conclusions: USA Subgroup

- Compared with placebo, in the USA patients, icosapent ethyl 4 grams per day resulted in statistically significant:
  - **31%** reductions in the primary and key secondary endpoints
  - **28%** to **47%** reductions in all prespecified hierarchical testing endpoints
  - **36%** reduction in total events, including a **37%** reduction in second events, a **37%** reduction in third events, and a **44%** reduction in 4th or more events
  - **30%** relative risk reduction and **2.6%** absolute risk reduction in all-cause mortality

Bhatt DL, Miller M, Brinton EA, et al. *Circulation.* 2019. Bhatt DL. AHA 2019, Philadelphia.

We thank the investigators, the study coordinators, and the 3,146 USA patients who participated in REDUCE-IT!

reduce-it USA

Circulation

CIRCULATION. 2019; [PUBLISHED ONLINE AHEAD OF PRINT]. DOI: 10.1161/CIRCULATIONAHA.119.044440.

REDUCE-IT USA: RESULTS FROM THE 3,146 PATIENTS RANDOMIZED IN THE UNITED STATES

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American Heart Association.


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