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Icosapent Ethyl Provides Consistent Cardiovascular Benefit in Patients with Diabetes in REDUCE-IT

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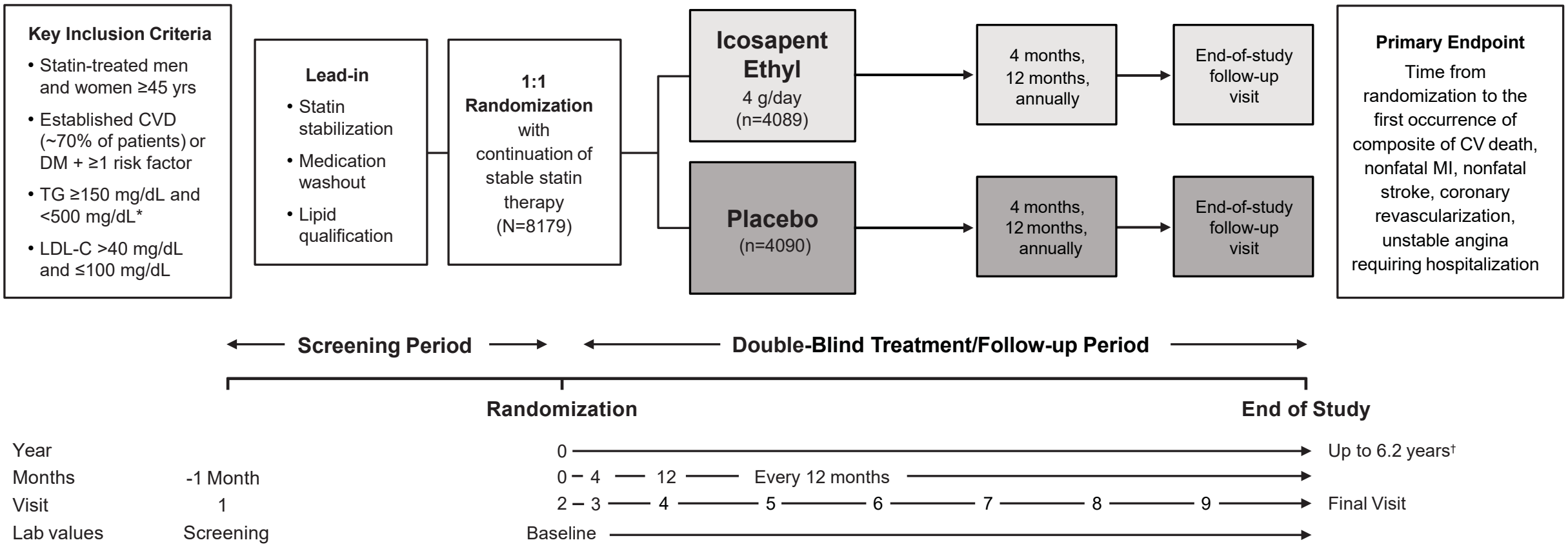
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, LevelEx, Medscape Cardiology, PhaseBio, PLx Pharma, 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; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), 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), MJH Life Sciences, 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, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, 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, Takeda.

This presentation may include off-label and/or investigational uses of drugs. REDUCE-IT was sponsored by Amarin Pharma, Inc.

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.

Primary and Key Secondary Composite Endpoints

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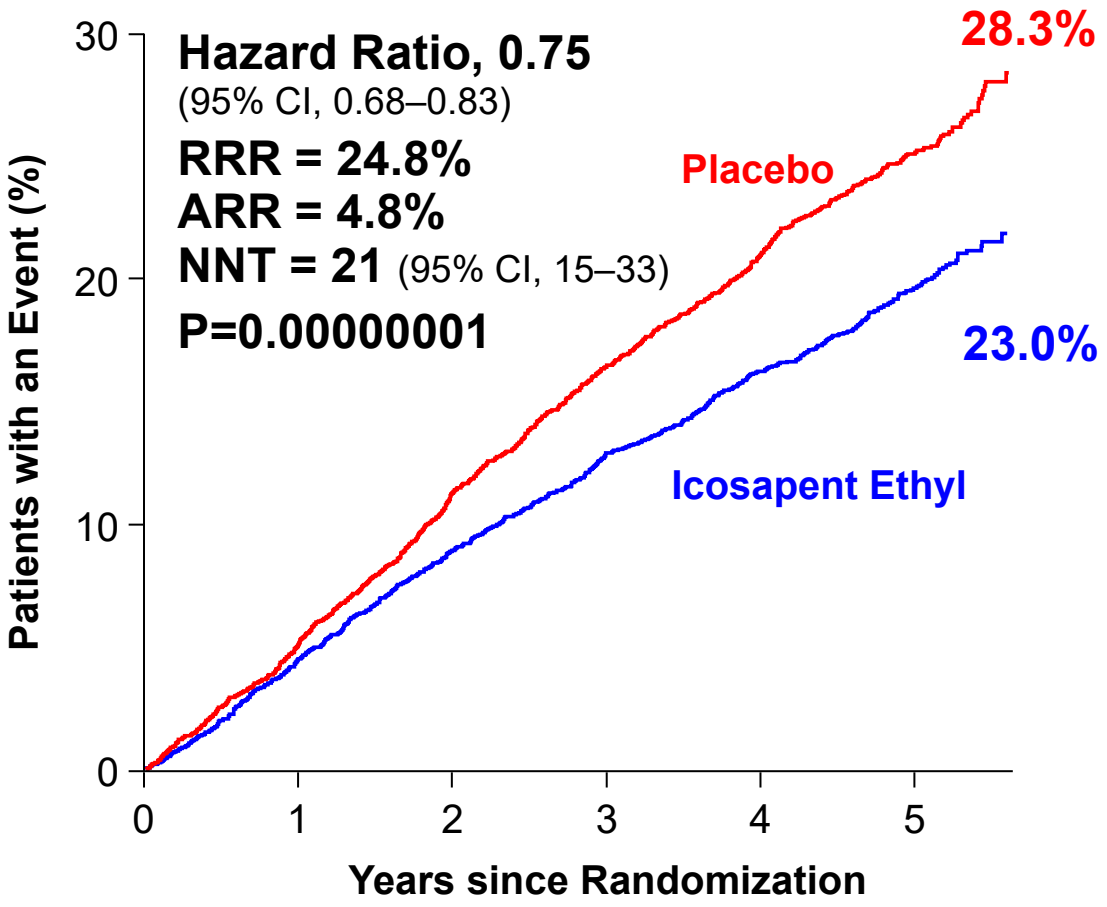
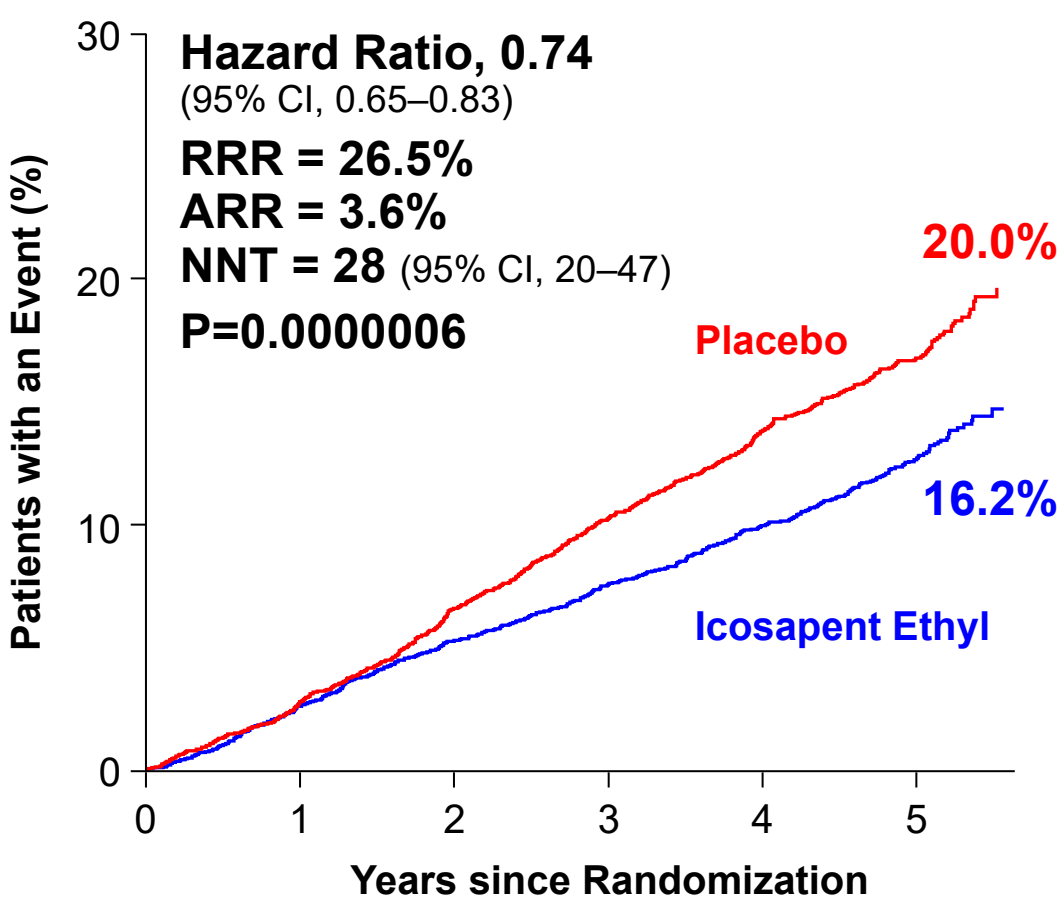
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

CV Death, MI, Stroke



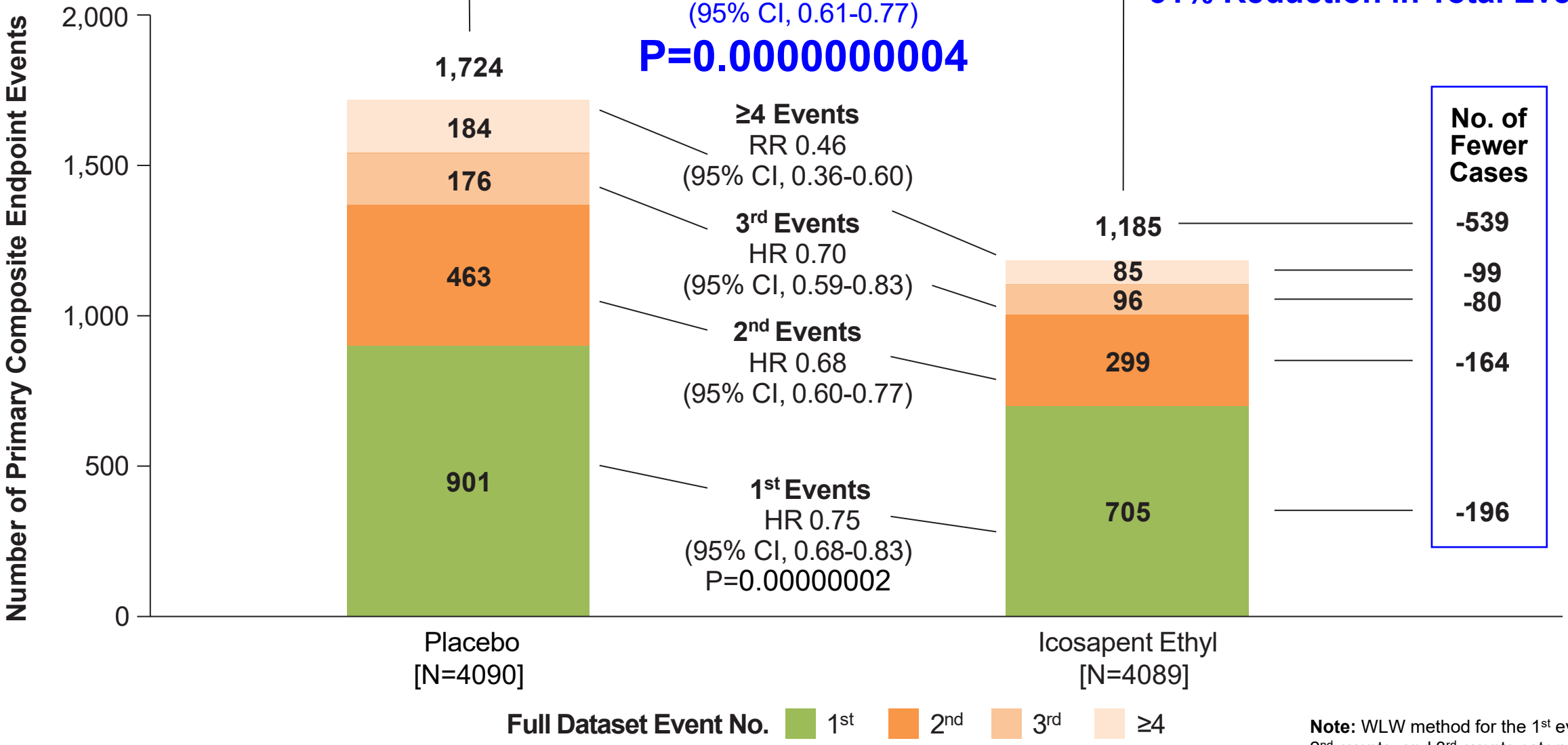
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

First and Subsequent Events – Full Data

reduce-it TOTAL EVENTS

RR 0.69
(95% CI, 0.61-0.77)
P=0.0000000004

31% Reduction in Total 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;73:2791-2802. Bhatt DL. ACC 2019, New Orleans.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Key Baseline Characteristics:

Diabetes Subgroup

	Icosapent Ethyl (N=2394)	Placebo (N=2393)	Overall (N=4787)	P value
Age (years), Median (Q1-Q3)	64.0 (58.0-70.0)	64.0 (58.0-70.0)	64.0 (58-70.0)	0.64
Female, n (%)	852 (35.6%)	877 (36.6%)	1729 (36.1%)	0.45
White, n (%)	2109 (88.1%)	2086 (87.2%)	4195 (87.6%)	0.33
Westernized Region, n (%)	1747 (73.0%)	1749 (73.1%)	3496 (73.0%)	0.93
CV Risk Category, n (%)				0.94
Established Cardiovascular Disease	1202 (50.2%)	1199 (50.1%)	2401 (50.2%)	
Diabetes + Risk Factors	1192 (49.8%)	1194 (49.9%)	2386 (49.8%)	
Ezetimibe Use, n (%)	124 (5.2%)	127 (5.3%)	251 (5.2%)	0.84
Statin Intensity, n (%)				0.42
Low	205 (8.6%)	203 (8.5%)	408 (8.5%)	
Moderate	1494 (62.4%)	1531 (64.0%)	3025 (63.2%)	
High	686 (28.7%)	645 (27.0%)	1331 (27.8%)	
Missing	9 (0.4%)	14 (0.6%)	23 (0.5%)	
BMI (Kg/m^2), Median (Q1-Q3)	32.0 (28.5-35.8)	31.9 (28.6-36.0)	32.0 (28.6-36.0)	0.82
Triglycerides (mg/dL), Median (Q1-Q3)	217.0 (177.0-271.5)	217.0 (176.0-275.5)	217.0 (176.5-274.0)	0.59
HDL-C (mg/dL), Median (Q1-Q3)	39.5 (34.5-45.3)	40.0 (34.5-46.0)	39.6 (34.5-45.5)	0.08
LDL-C (mg/dL), Median (Q1-Q3)	73.0 (60.0-87.0)	75.0 (62.0-89.0)	74.0 (61.0-88.0)	0.01
Triglycerides Category, n (%)				0.77
<150 mg/dL	249 (10.4%)	234 (9.8%)	483 (10.1%)	
150 to <200 mg/dL	693 (28.9%)	696 (29.1%)	1389 (29.0%)	
≥200 mg/dL	1449 (60.5%)	1462 (61.1%)	2911 (60.8%)	
Glucose (mg/dL), Median (Q1-Q3)	139.0 (117.0-169.0)	138.0 (115.0-171.0)	139.0 (116.0-170.0)	0.75
HbA1c (%), Median (Q1-Q3)	7.0 (6.3-7.8)	7.0 (6.3-7.9)	7.0 (6.3-7.9)	0.68

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Number of Baseline Anti-Diabetes Medications: Diabetes Subgroup

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Anti-Diabetes Medications Taken at Baseline, n (%)	Icosapent Ethyl (N=2394)	Placebo (N=2393)	Overall (N=4787)
No Anti-Diabetes Medications	221 (9.2)	208 (8.7)	429 (9.0)
Anti-Diabetes Medications	2173 (90.8)	2185 (91.3)	4358 (91.0)
One Anti-Diabetes Medication	951 (39.7)	1038 (43.4)	1989 (41.6)
Two Anti-Diabetes Medication	806 (33.7)	792 (33.1)	1598 (33.4)
Three Anti-Diabetes Medication	347 (14.5)	288 (12.0)	635 (13.3)
Four or more Anti-Diabetes Medications	69 (2.9)	67 (2.8)	136 (2.8)

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population with diabetes at baseline (N).

Bhatt DL, Brinton EA, Miller M, et al. ADA 2020, Chicago (virtual).

Time to First and Total Primary and Key Secondary Endpoint Events:
Diabetes Subgroup: N=4787

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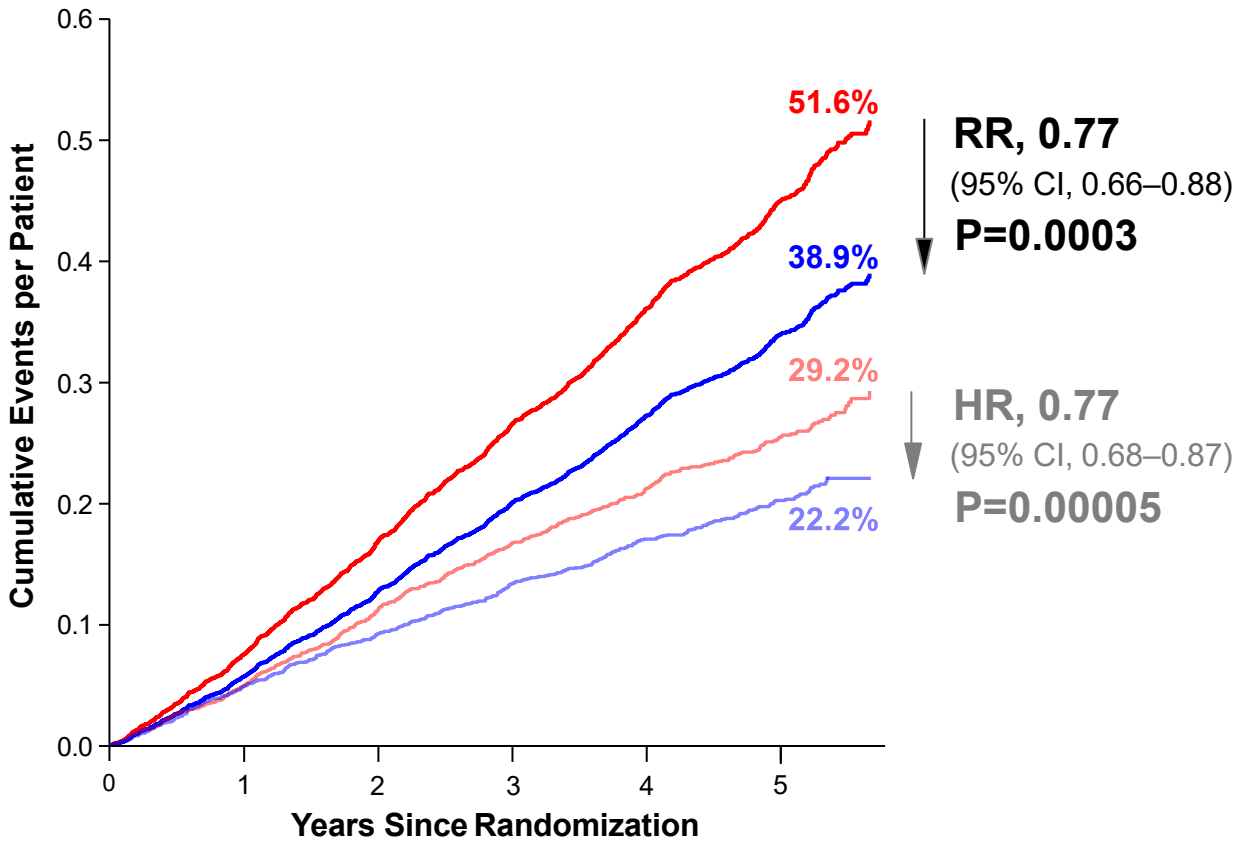
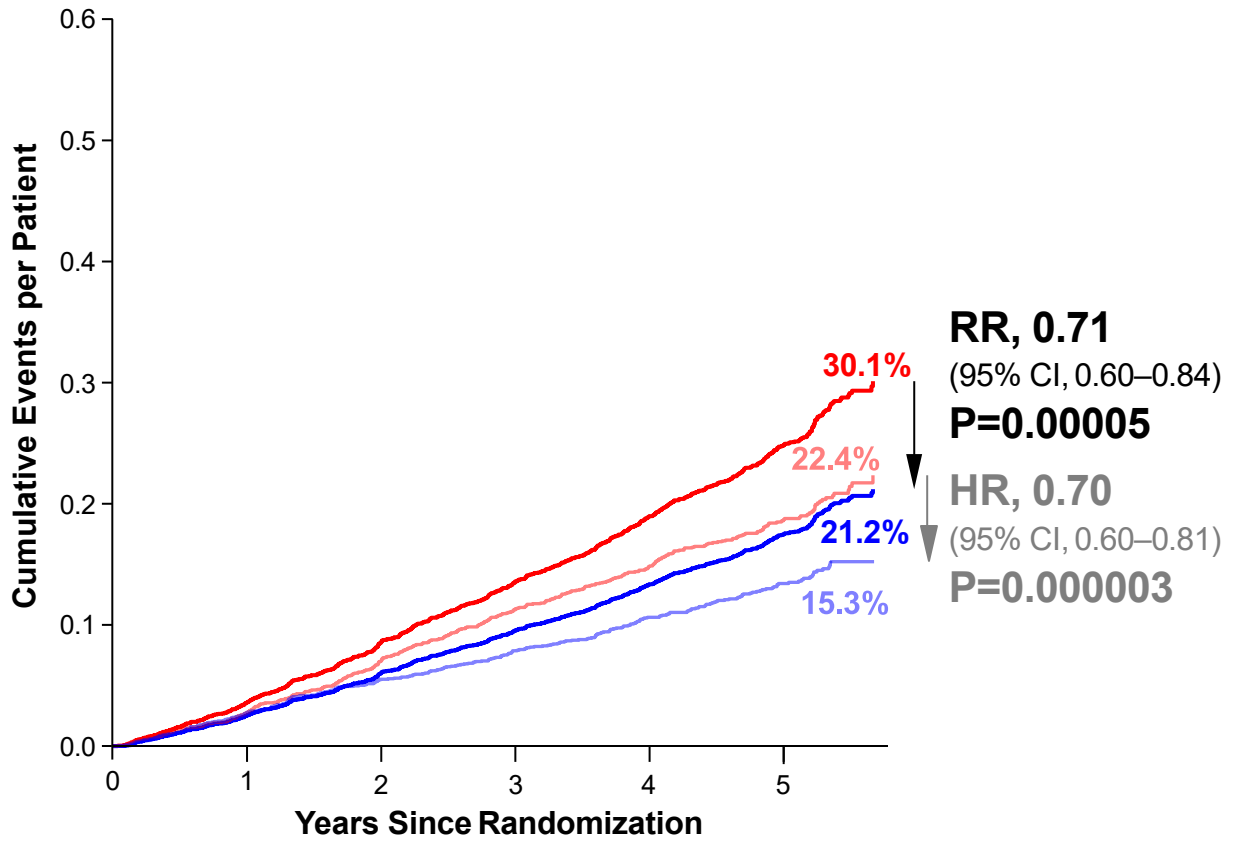
Primary Composite Endpoint



Key Secondary Composite Endpoint



Placebo: Total Events — Icosapent Ethyl: Total Events — Placebo: First Events — Icosapent Ethyl: First Events

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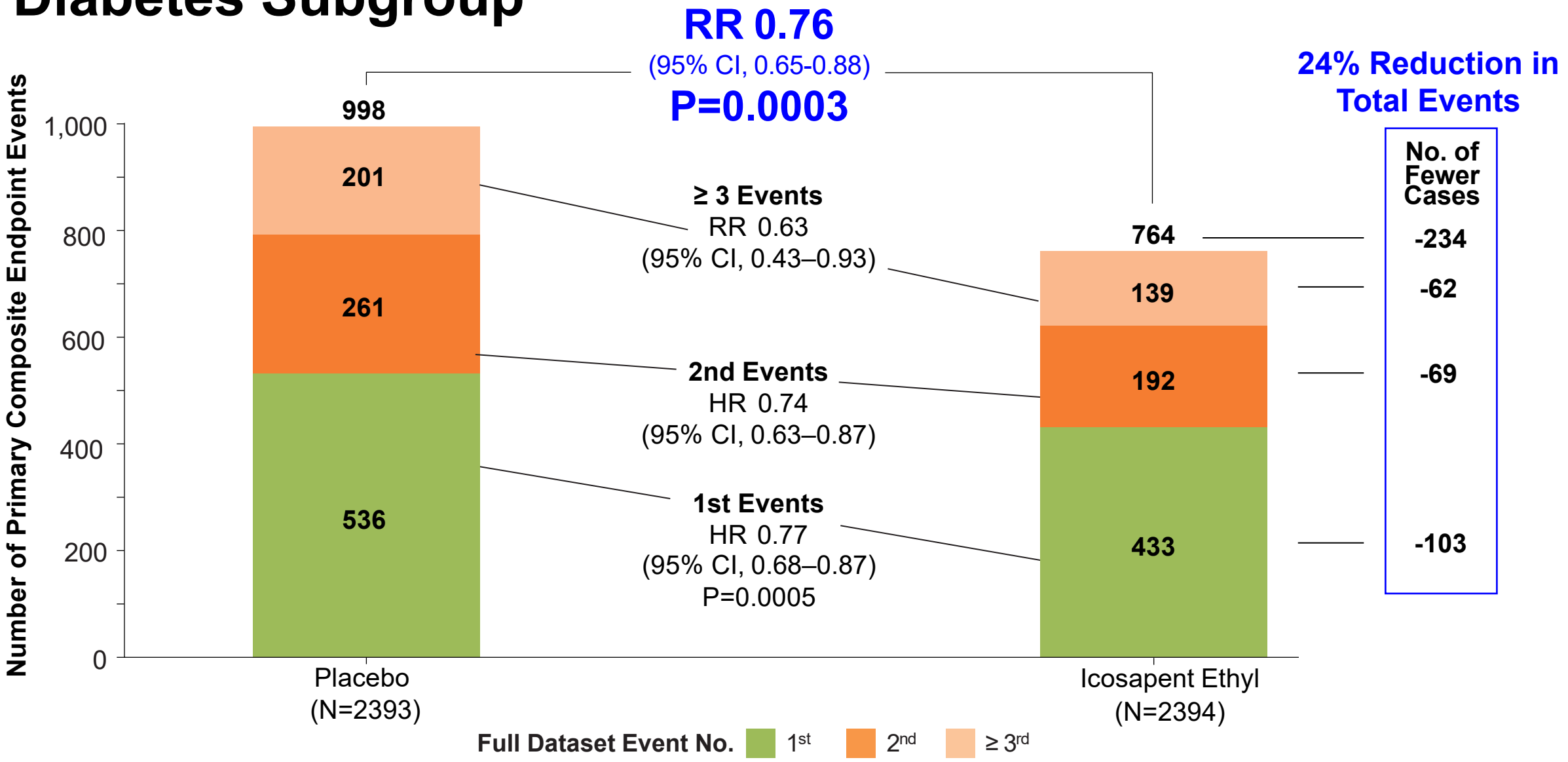
Total events analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single event.

First and Subsequent Events Full Dataset
Diabetes Subgroup



Bhatt DL, Brinton EA, Miller M, et al. ADA 2020, Chicago (virtual).

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

Prespecified Hierarchical Testing:
Diabetes Subgroup

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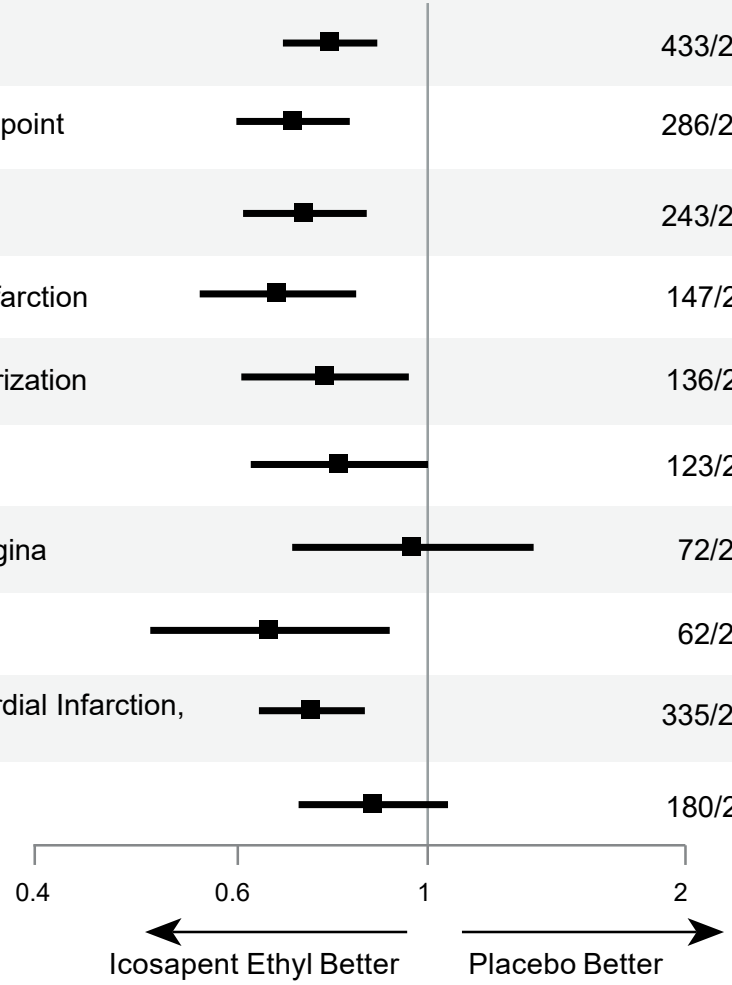
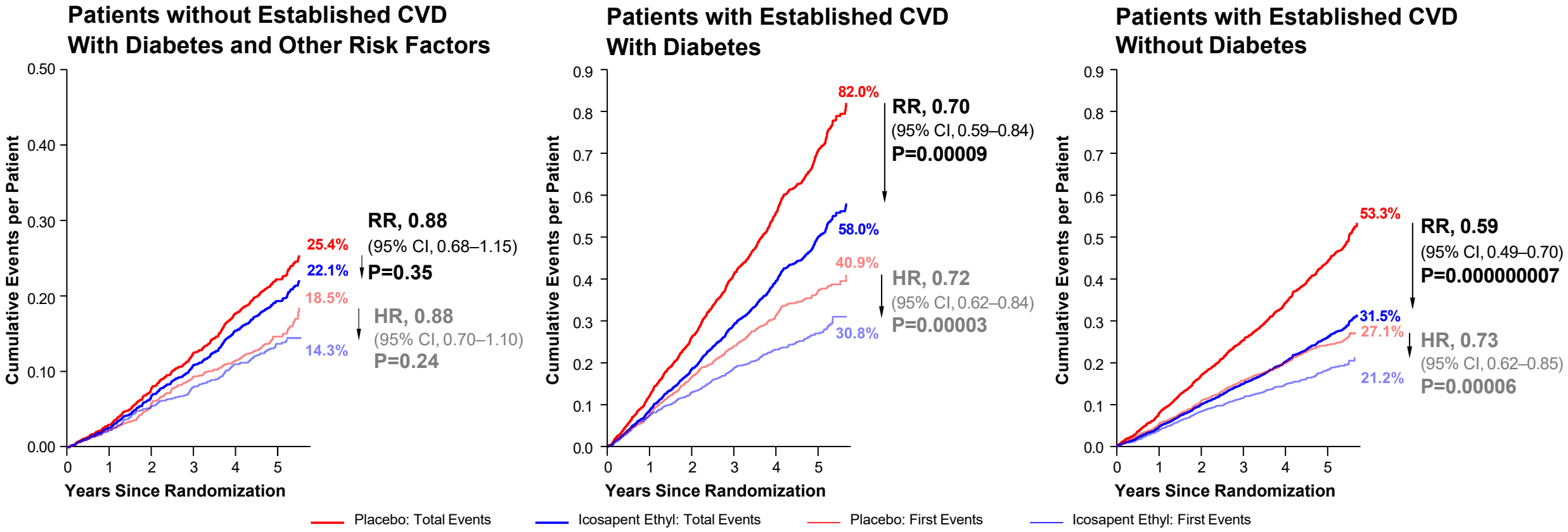
Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	Relative Risk Reduction	P-value
Primary Composite Endpoint		433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68–0.87)	23%	<0.0001
Key Secondary Composite Endpoint		286/2394 (11.9%)	391/2393 (16.3%)	0.70 (0.60–0.81)	30%	<0.0001
Cardiovascular Death or Nonfatal Myocardial Infarction		243/2394 (10.2%)	324/2393 (13.5%)	0.72 (0.61–0.85)	28%	<0.0001
Fatal or Nonfatal Myocardial Infarction		147/2394 (6.1%)	212/2393 (8.9%)	0.67 (0.54–0.83)	33%	0.0002
Urgent or Emergent Revascularization		136/2394 (5.7%)	173/2393 (7.2%)	0.76 (0.61–0.95)	24%	0.02
Cardiovascular Death		123/2394 (5.1%)	151/2393 (6.3%)	0.79 (0.62–1.00)	21%	0.05
Hospitalization for Unstable Angina		72/2394 (3.0%)	74/2393 (3.1%)	0.96 (0.69–1.33)	4%	0.81
Fatal or Non-Fatal Stroke		62/2394 (2.6%)	92/2393 (3.8%)	0.65 (0.47–0.90)	35%	0.009
Total Mortality/Nonfatal Myocardial Infarction, or Nonfatal Stroke		335/2394 (14.0%)	435/2393 (18.2%)	0.73 (0.64–0.84)	27%	<0.0001
Total Mortality		180/2394 (7.5%)	202/2393 (8.4%)	0.86 (0.71–1.06)	14%	0.15



Bhatt DL, Brinton EA, Miller M, et al. ADA 2020, Chicago (virtual).

Time to First and Total Primary Endpoint Events by CV Risk Category and Diabetes Status at Baseline



Interaction P-value between patients with established CVD with diabetes and patients with established CVD without diabetes = 0.98
Interaction P-value between patients with diabetes and other risk factors, patients with established CVD with diabetes, and patients with established CVD without diabetes = 0.32

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Safety: Diabetes Subgroup

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Safety was generally consistent with the full study, including increases in atrial fibrillation/flutter (3.5% vs 2.2%; p=0.01) and bleeding (13.1% vs 10.9%; p=0.02).

Serious bleeding was not significantly different (3.2% vs 2.5%; p=0.19).

There were no meaningful between-group differences in HbA1c or glucose control across study visits, including placebo-corrected median changes from baseline to year 1 for HbA1c (0%, p=0.19) and glucose (-0.06 mmol/L, p=0.34).

Limitations

The study was not powered for subgroup analyses.

While cardiovascular risk category (established cardiovascular disease or diabetes plus risks) were stratification factors, the presence of diabetes within the established cardiovascular disease cohort was not.

These data include both pre-specified and *post hoc* analyses.

The study was not designed for in-depth biomarker analyses. Glucose and HbA1c were infrequently collected, generally on an annual basis.

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced both first and total primary endpoint events in patients with diabetes at baseline by **23%** and **24%**, respectively.

For the key secondary endpoint of hard MACE, reductions for first and total events were **30%** and **29%**, respectively.

Reductions were consistent and robust across the prespecified hierarchy of endpoints, among patients with diabetes with or without cardiovascular disease, as well as those with established CVD and no diabetes at baseline.

These data highlight the substantial impact of icosapent ethyl on the underlying atherothrombotic burden in the at-risk **REDUCE-IT** population, both in those with but also in those without diabetes mellitus.

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

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