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Reductions in Ischemic Stroke with Icosapent Ethyl: Insights From REDUCE-IT

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

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Disclosures

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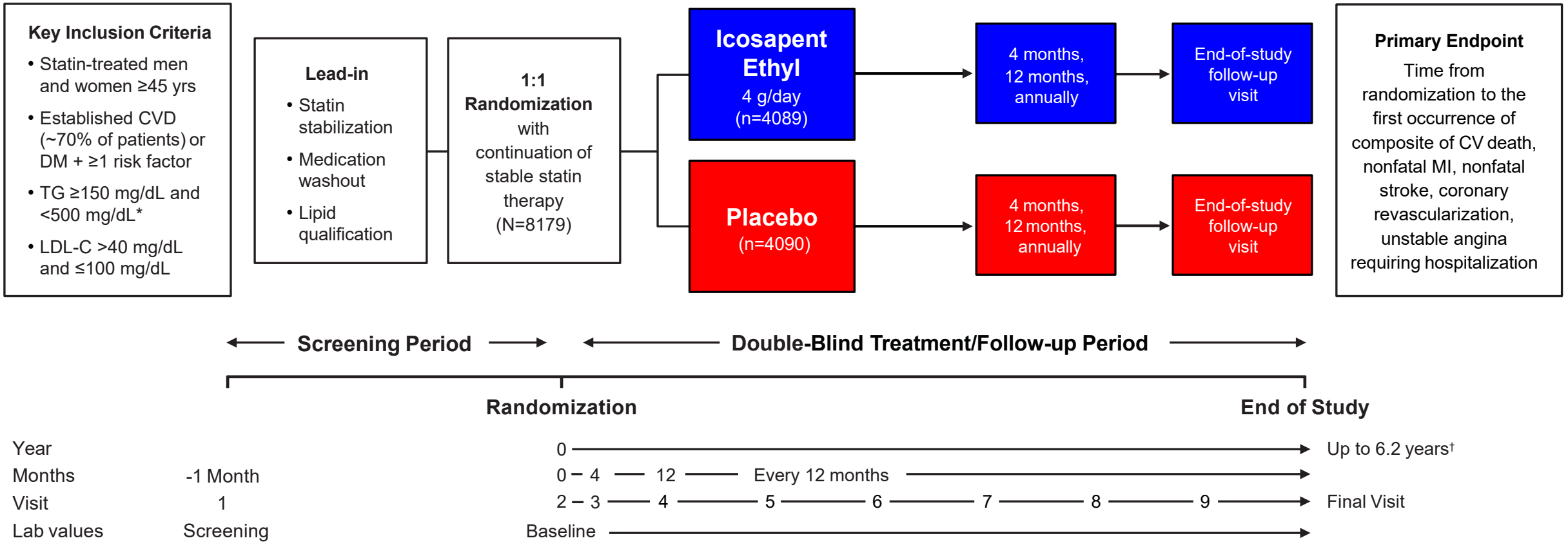
REDUCE-IT Design



*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).

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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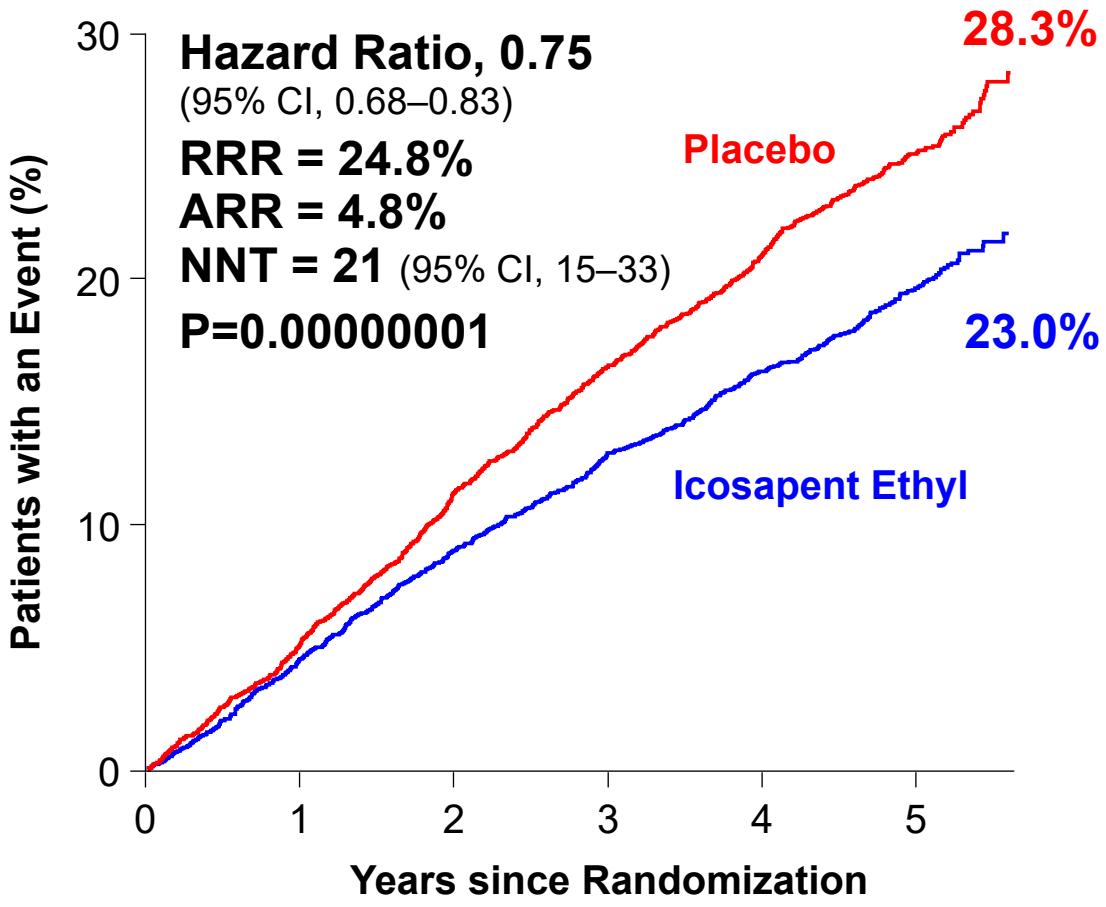
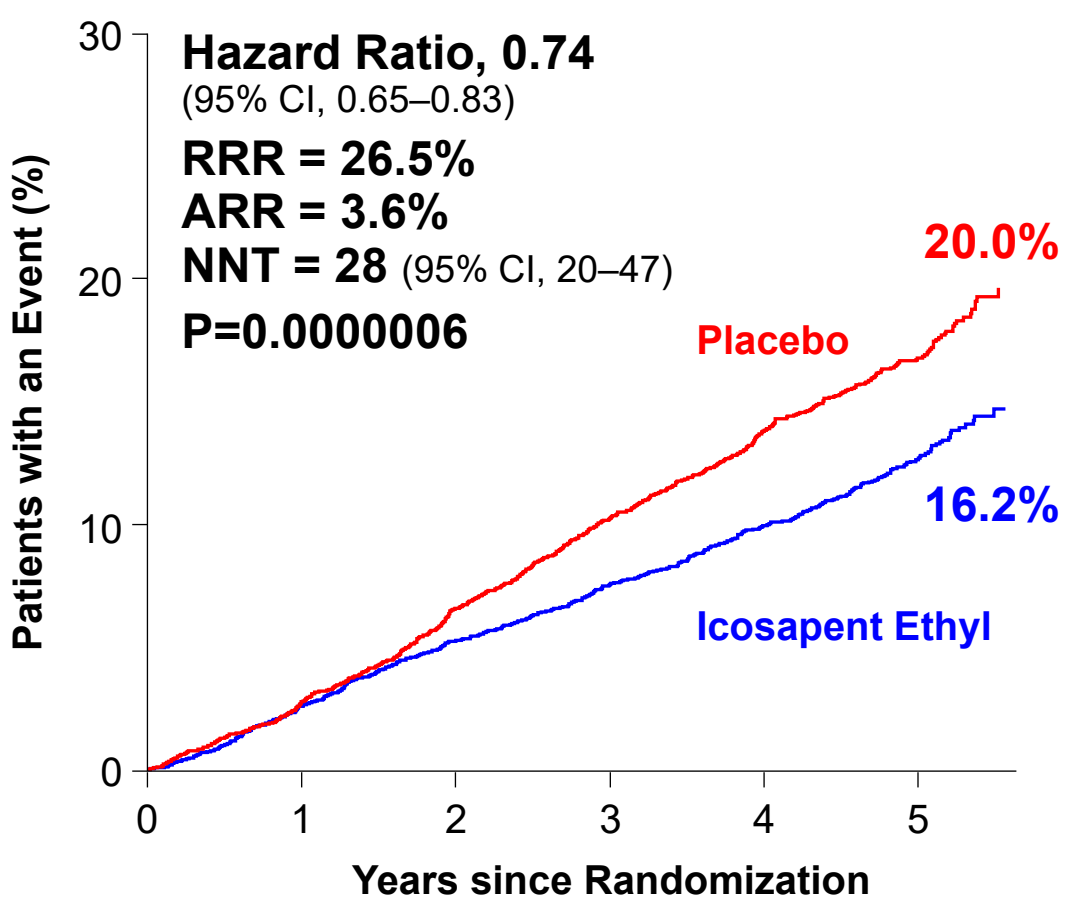
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

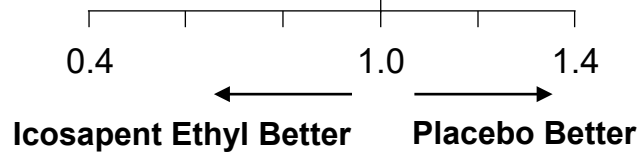
CV Death, MI, Stroke



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

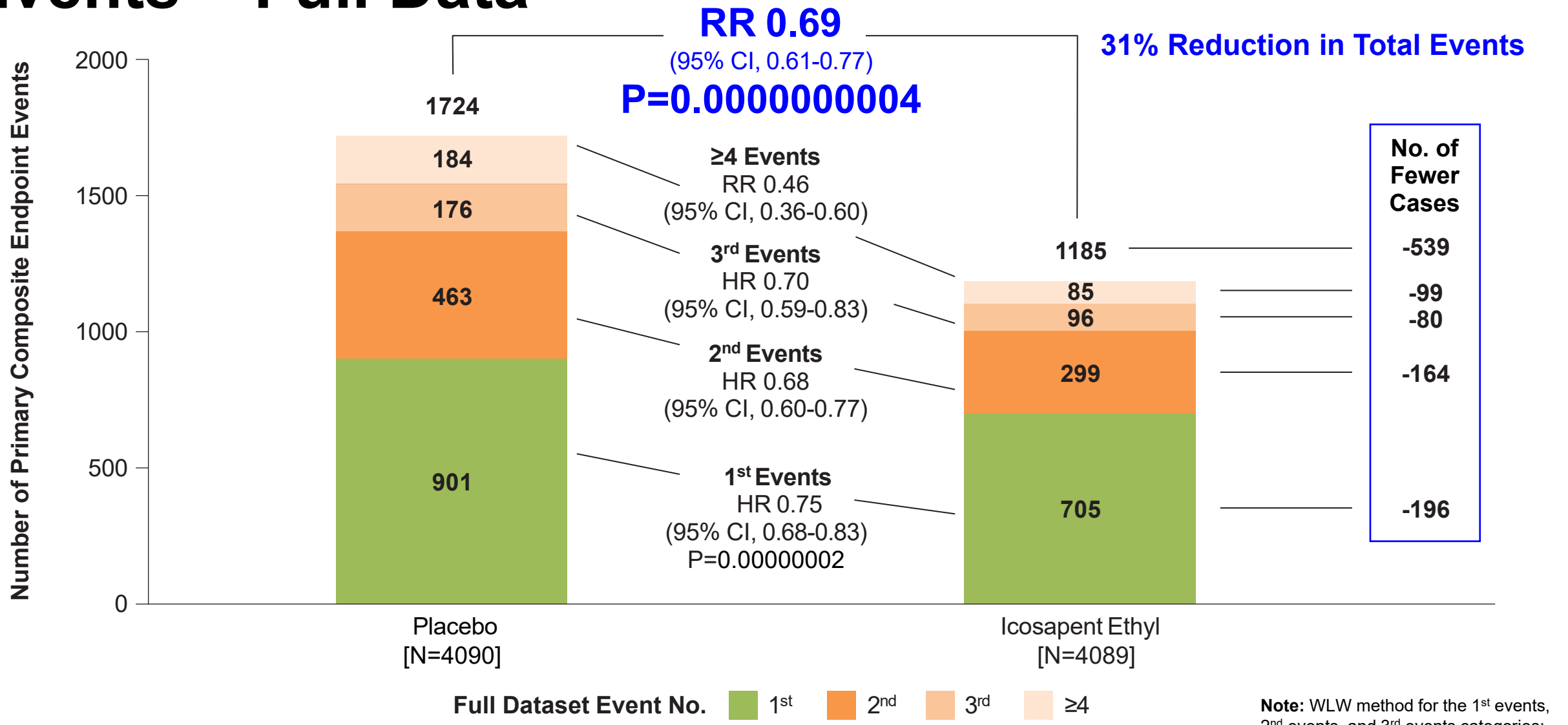
Prespecified Hierarchical Testing

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% ▼	<0.0001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26% ▼	<0.0001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25% ▼	<0.0001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31% ▼	<0.0001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35% ▼	<0.0001
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.

Primary Endpoint 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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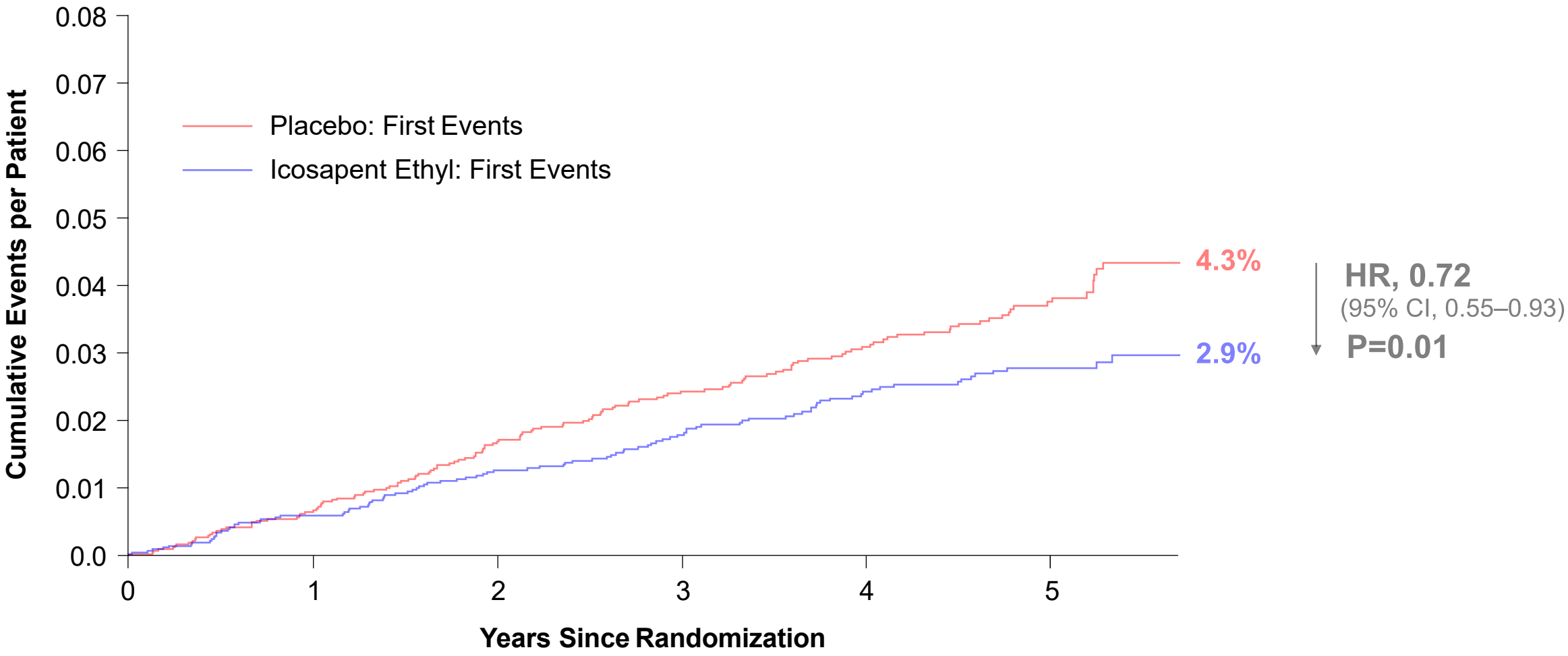
Icosapent Ethyl Reduced First Strokes



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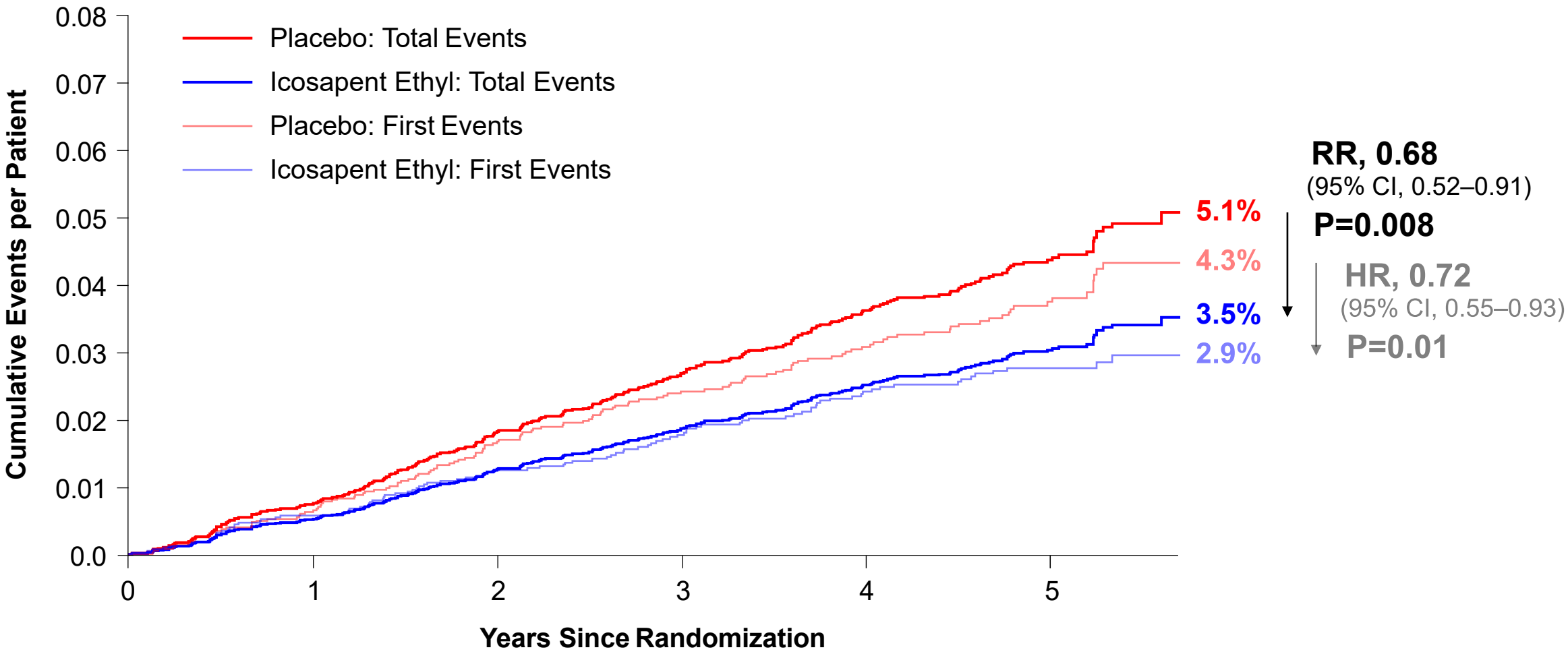
Icosapent Ethyl Reduced First and Total Strokes



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Stroke by Type

Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	Icosapent Ethyl, Rate per 1000 Patient Years	Placebo, Rate per 1000 Patient Years
Any stroke	98 (2.4%)	134 (3.3%)	0.72 (0.55, 0.93)	5.6	7.8
Nonfatal vs. fatal stroke					
Nonfatal stroke	85 (2.1%)	118 (2.9%)	0.71 (0.54, 0.94)	4.9	6.9
Fatal stroke	14 (0.3%)	18 (0.4%)	0.77 (0.38, 1.54)	0.8	1.0
Ischemic vs. hemorrhagic stroke					
Ischemic stroke	80 (2.0%)	122 (3.0%)	0.64 (0.49, 0.85)	4.6	7.1
Hemorrhagic stroke	13 (0.3%)	10 (0.2%)	1.28 (0.56, 2.93)	0.7	0.6

Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is 1000 × n/pt-yrs subjects at-risk.

Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

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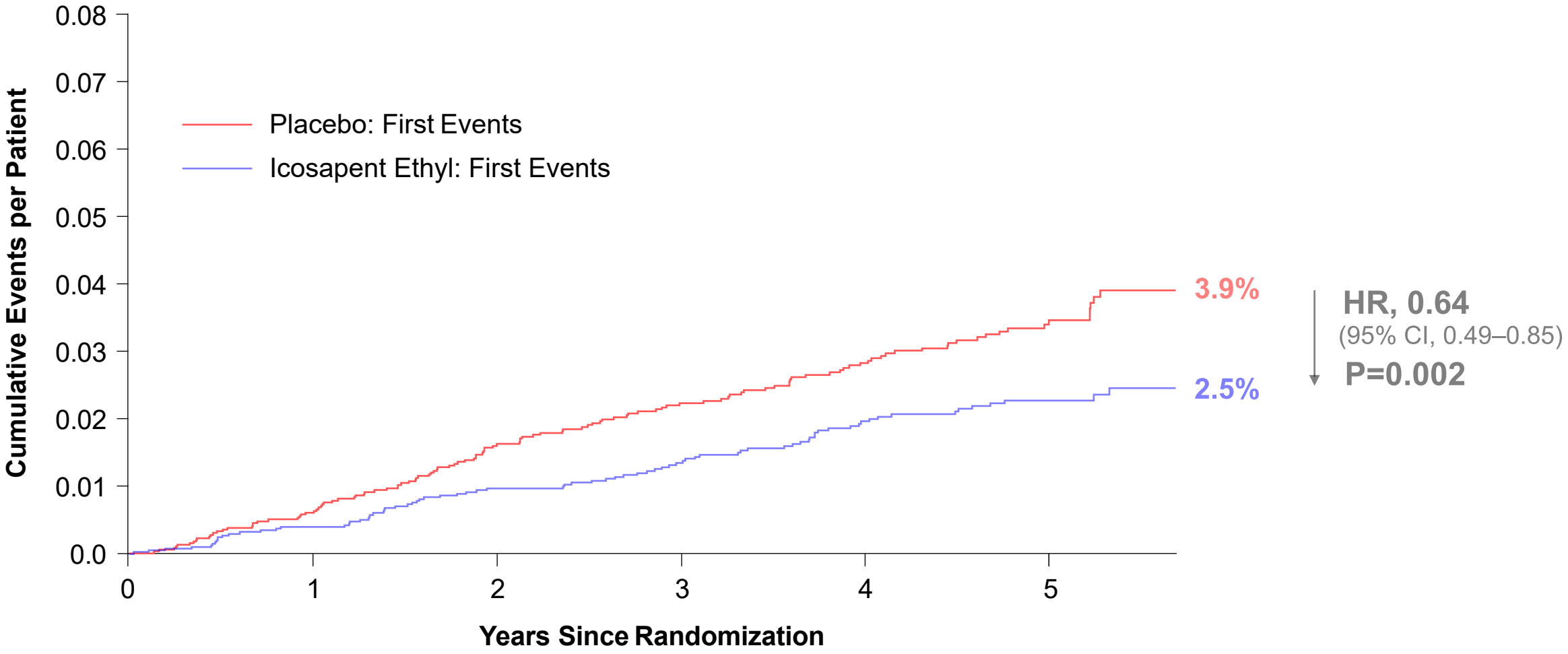
Icosapent Ethyl Reduced First Ischemic Strokes



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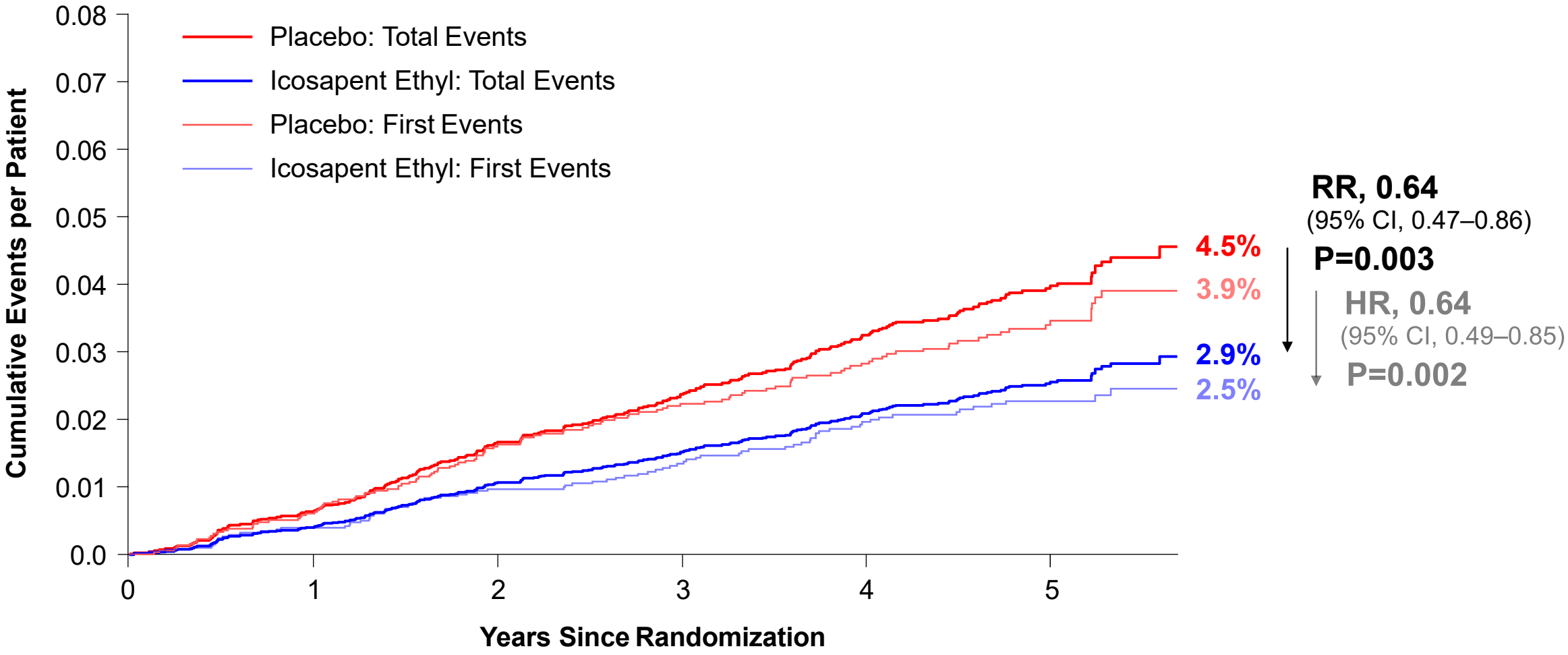
Icosapent Ethyl Reduced First and Total Ischemic Strokes



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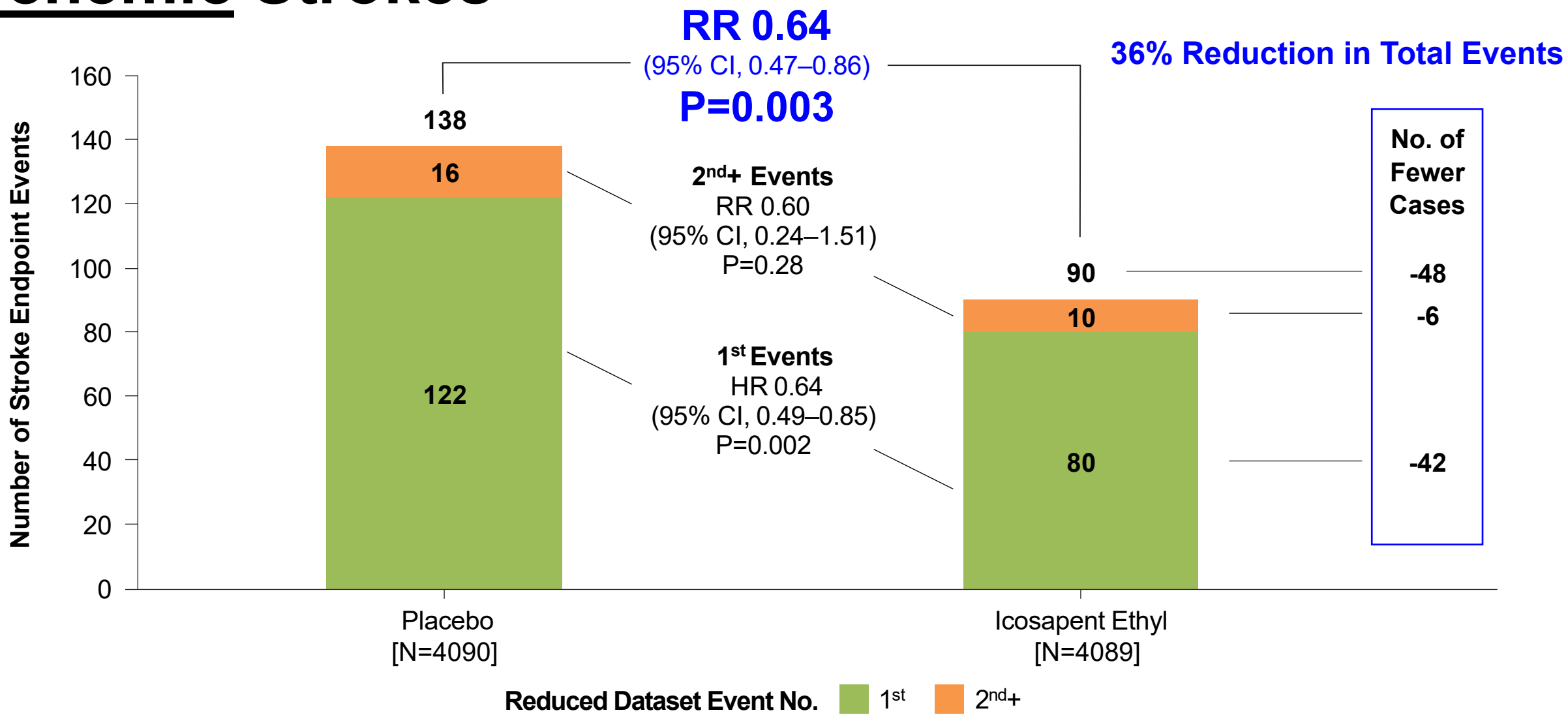
Icosapent Ethyl Reduced First and Total Ischemic Strokes



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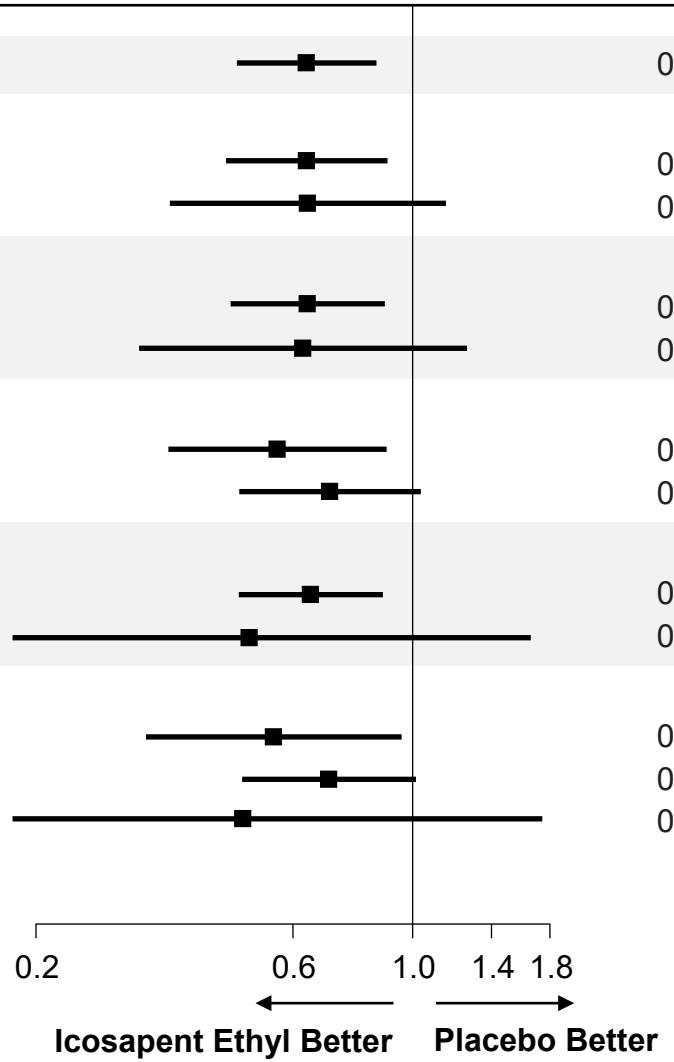
Note: WLW method for the 1st events, negative binomial model for ≥2nd events and overall treatment comparison.

Total Ischemic Strokes by Subgroup:
Stratification factors, region, statin use

Subgroup	Icosapent Ethyl, Rate per 1000 Patient Years	Placebo, Rate per 1000 Patient Years	Rate Ratio (95% CI)	P-value for Interaction
All patients	5.1	7.9	0.64 (0.47, 0.86)	
Risk stratum				0.98
Established CV disease	5.4	8.4	0.64 (0.45, 0.90)	
Diabetes plus CV risk	4.5	7.0	0.64 (0.35, 1.15)	
Region				0.96
Westernized	6.0	9.2	0.64 (0.46, 0.89)	
Non-Westernized	2.9	4.8	0.63 (0.31, 1.26)	
From the United States				0.47
Yes	6.1	10.4	0.56 (0.35, 0.90)	
No	4.5	6.5	0.70 (0.48, 1.04)	
Ezetimibe use				0.69
No	5.1	7.8	0.65 (0.48, 0.88)	
Yes	5.1	9.6	0.50 (0.15, 1.65)	
Baseline statin intensity				0.75
High	5.4	9.4	0.55 (0.32, 0.96)	
Moderate	5.1	7.3	0.70 (0.48, 1.02)	
Low	3.8	7.3	0.49 (0.14, 1.74)	



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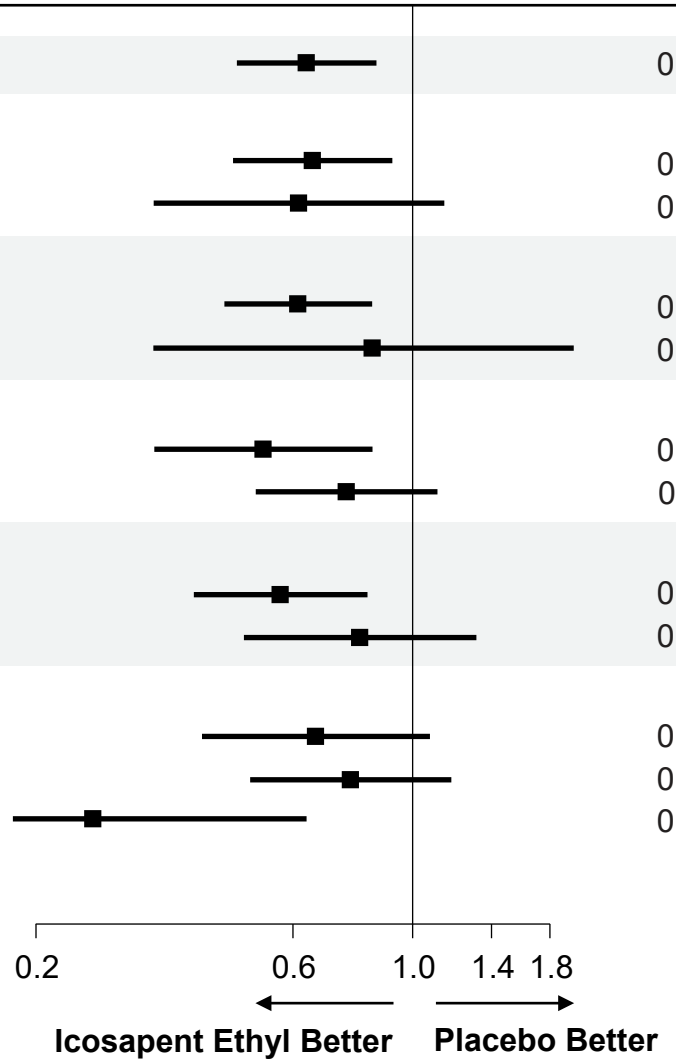
Total Ischemic Strokes by Subgroup:
Demographics and disease characteristics

Subgroup	Icosapent Ethyl, Rate per 1000 Patient Years	Placebo, Rate per 1000 Patient Years	Rate Ratio (95% CI)	P-value for Interaction
All patients	5.1	7.9	0.64 (0.47, 0.86)	
Sex				0.86
Male	5.1	7.7	0.65 (0.46, 0.92)	
Female	5.2	8.5	0.62 (0.33, 1.14)	
Race				0.48
White	5.0	8.0	0.61 (0.45, 0.84)	
Other	6.3	7.7	0.84 (0.33, 2.15)	
Age				0.25
<65 yr	3.5	6.6	0.53 (0.33, 0.84)	
≥65 yr	7.1	9.5	0.75 (0.51, 1.11)	
Diabetes at baseline				0.29
Yes	5.6	9.7	0.57 (0.39, 0.82)	
No	4.4	5.5	0.80 (0.49, 1.31)	
Baseline estimated GFR				0.10
<60 mL/min/1.73 m²	10.7	15.5	0.66 (0.41, 1.08)	
≥60 to <90 mL/min/1.73 m²	4.5	5.9	0.77 (0.50, 1.18)	
≥90 mL/min/1.73 m²	1.4	5.7	0.26 (0.10, 0.63)	



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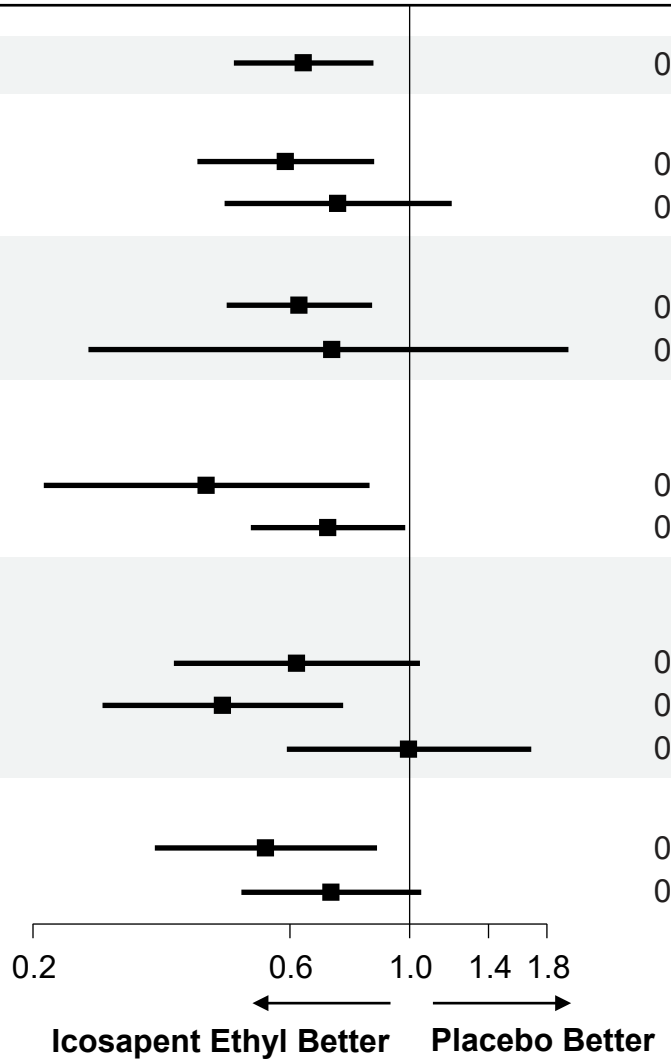
Total Ischemic Strokes by Subgroup: Biomarkers

Subgroup	Icosapent Ethyl, Rate per 1000 Patient Years	Placebo, Rate per 1000 Patient Years	Rate Ratio (95% CI)	P-value for Interaction
All patients	5.1	7.9	0.64 (0.47, 0.86)	
Baseline triglycerides				0.49
≥200 mg/dL	5.3	8.8	0.59 (0.40, 0.86)	
<200 mg/dL	4.9	6.8	0.74 (0.45, 1.20)	
Baseline triglycerides				0.83
≥150 mg/dL	5.2	8.1	0.63 (0.46, 0.86)	
<150 mg/dL	4.6	6.5	0.72 (0.26, 2.05)	
Baseline triglycerides ≥200 mg/dL and HDL cholesterol ≤35 mg/dL				0.17
Yes	4.6	10.6	0.42 (0.21, 0.84)	
No	5.2	7.3	0.71 (0.51, 0.99)	
Baseline LDL cholesterol (derived) in thirds				0.12
≤67 mg/dL	4.8	7.7	0.62 (0.36, 1.04)	
>67 to ≤84 mg/dL	4.3	9.6	0.45 (0.27, 0.76)	
>84 mg/dL	6.3	6.5	0.99 (0.59, 1.68)	
Baseline high-sensitivity CRP				0.37
≤2 mg/L	3.9	7.2	0.54 (0.34, 0.87)	
>2 mg/L	6.2	8.6	0.71 (0.49, 1.05)	



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Safety Analyses

No differences were observed between icosapent ethyl and placebo in overall tolerability or adverse events.

More bleeding occurred with icosapent ethyl versus placebo, but there were no significant differences in hemorrhagic stroke.

More atrial fibrillation/flutter occurred with icosapent ethyl versus placebo.

Limitations

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

REDUCE-IT was designed and powered for the primary composite endpoint, of which stroke was one of five prespecified components; it was not powered for subgroup analyses.

Stroke was a prespecified secondary endpoint within the testing hierarchy; ischemic stroke was a prespecified tertiary endpoint; stroke subgroup analyses were *post hoc*.

No information was collected on stroke related disability, such as Rankin scores.

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced first and total strokes by **28%** and **32%**, respectively.

Icosapent ethyl significantly reduced first and total ischemic strokes each by **36%**, without increasing hemorrhagic stroke, in statin-treated patients with elevated cardiovascular risk.

Across multiple subgroups, there were generally consistent reductions in ischemic stroke.

EPA-based therapy with icosapent ethyl represents a novel approach to stroke reduction.

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