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Reduction of Revascularization in Patients with Hypertriglyceridemia with Icosapent Ethyl: Insights from REDUCE-IT REVASC

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

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Disclosures

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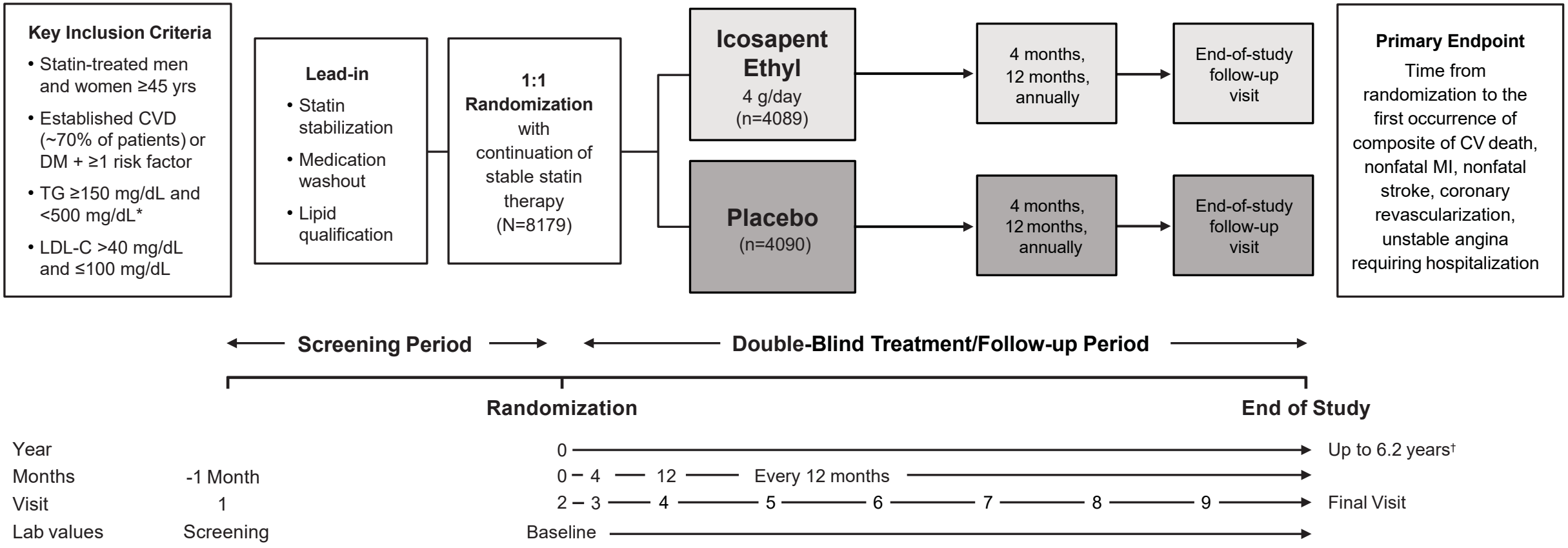
This presentation may include off-label and/or investigational uses of drugs. REDUCE-IT was sponsored by Amarin Pharma, Inc.

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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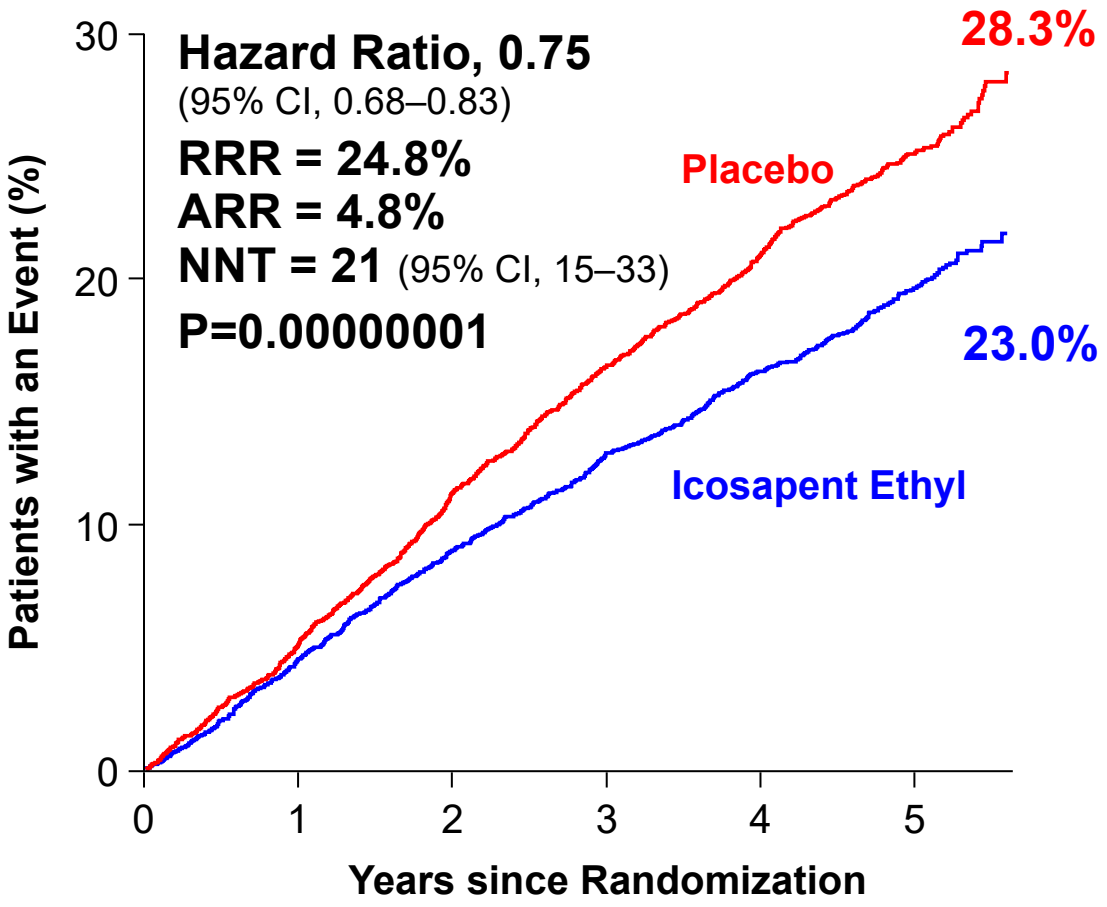
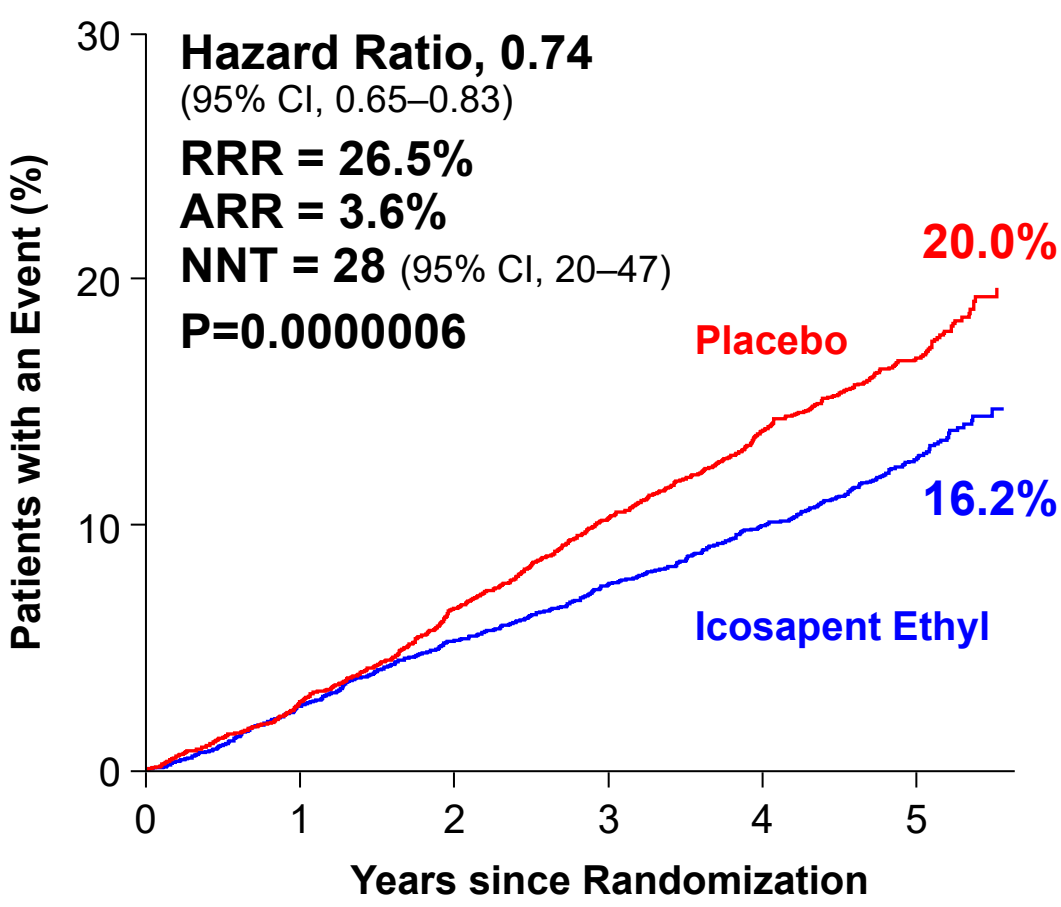
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

CV Death, MI, Stroke



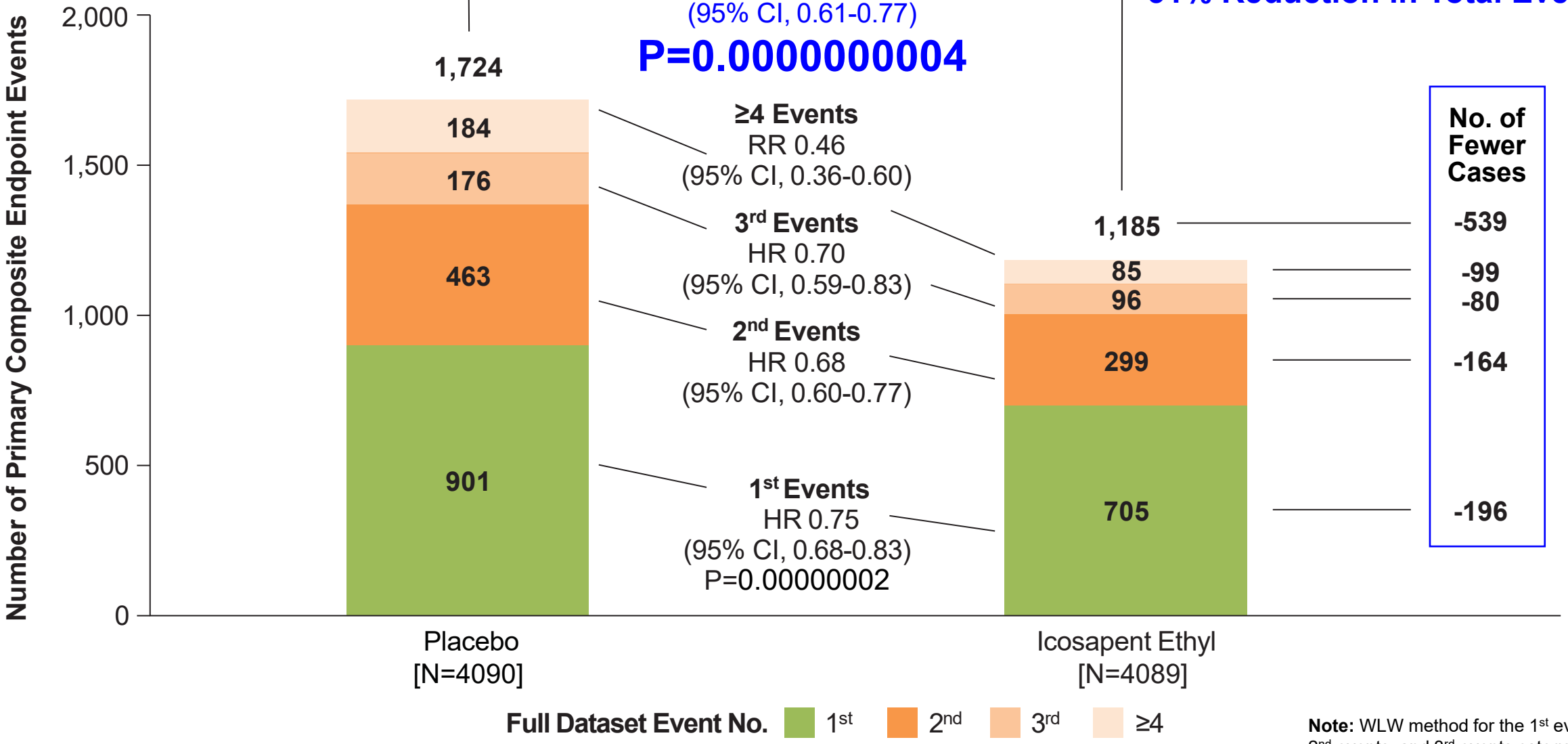
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

First and Subsequent Events – Full Data

reduce-it TOTAL EVENTS

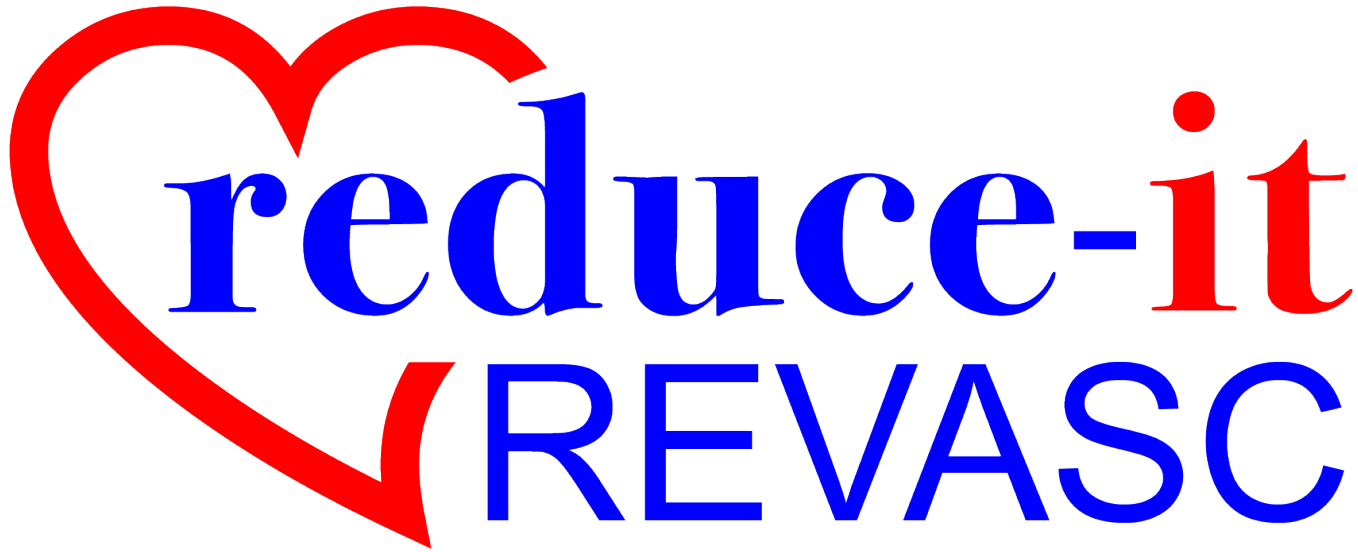
RR 0.69
(95% CI, 0.61-0.77)
P=0.0000000004

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

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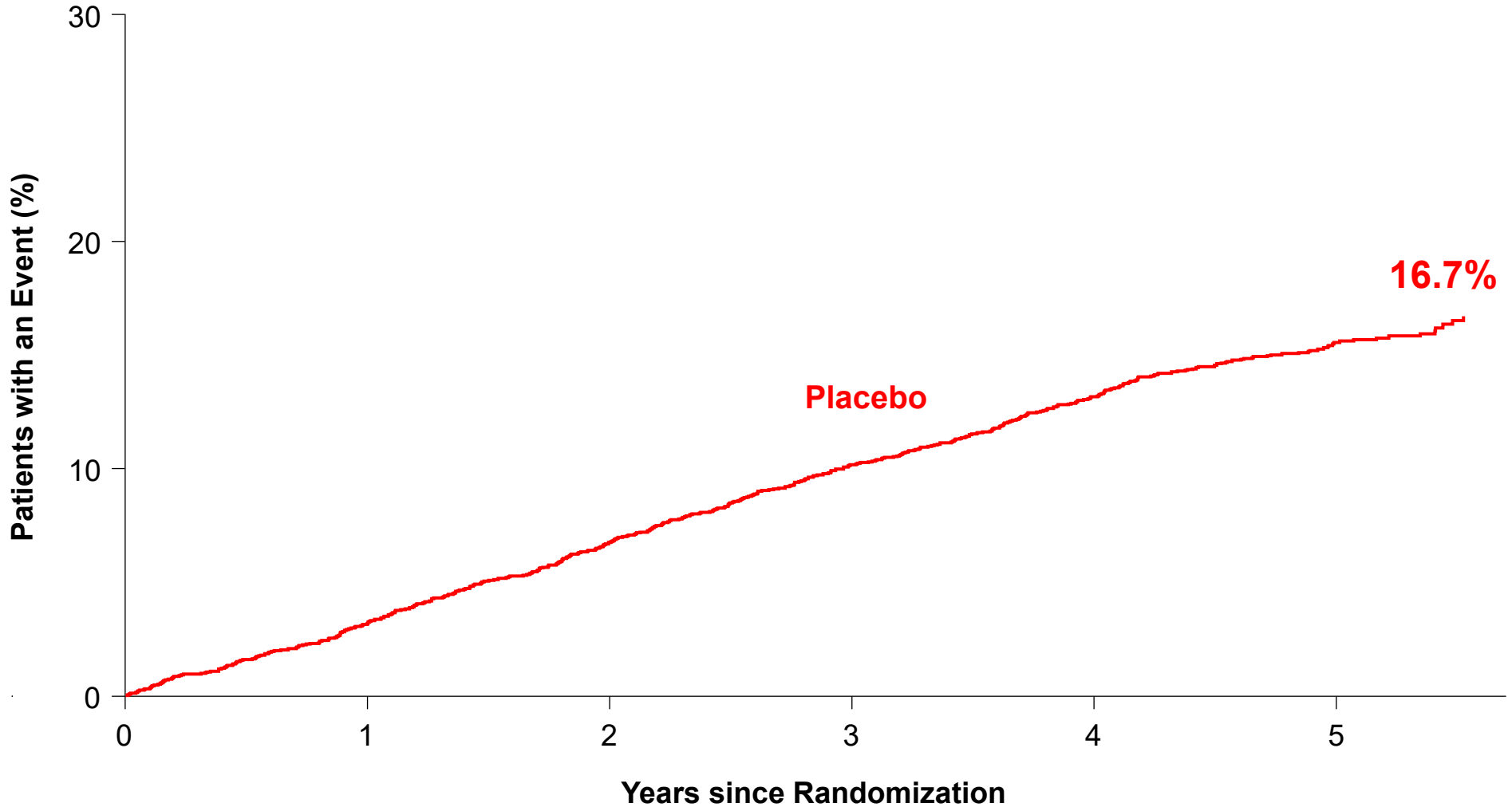
	In Study Revasc (N=920)	No In Study Revasc (N=7259)	Overall (N=8179)	P value
Age (years), Min-Max	64.0 (45.0-85.0)	64.0 (44.0-92.0)	64.0 (44.0-92.0)	0.58
Female, n (%)	170 (18.5%)	2187 (30.1%)	2357 (28.8%)	<0.0001
White, n (%)	847 (92.1%)	6532 (90.0%)	7379 (90.2%)	0.05
Westernized Region, n (%)	769 (83.6%)	5042 (69.5%)	5811 (71.0%)	<0.0001
CV Risk Category, n (%)				<0.0001
Established Cardiovascular Disease	770 (83.7%)	5015 (69.1%)	5785 (70.7%)	
Diabetes + Risk Factors	150 (16.3%)	2244 (30.9%)	2394 (29.3%)	
Ezetimibe Use, n (%)	86 (9.3%)	438 (6.0%)	524 (6.4%)	0.0001
Statin Intensity, n (%)				0.03
Low	52 (5.7%)	469 (6.5%)	521 (6.4%)	
Moderate	548 (59.6%)	4560 (62.8%)	5108 (62.5%)	
High	319 (34.7%)	2197 (30.3%)	2516 (30.8%)	
Missing	1 (0.1%)	33 (0.5%)	34 (0.4%)	
Type 2 Diabetes, n (%)	509 (55.3%)	4221 (58.1%)	4730 (57.8%)	0.10
Triglycerides (mg/dL), Median (Q1-Q3)	221.3 (178.5-284.3)	215.5 (175.5-271.5)	216.0 (176.0-272.5)	0.02
HDL-C (mg/dL), Median (Q1-Q3)	39.0 (33.5-44.5)	40.0 (35.0-46.0)	40.0 (35.0-46.0)	<0.0001
LDL-C (mg/dL), Median (Q1-Q3)	75.0 (63.0-89.0)	75.0 (62.0-89.0)	75.0 (62.0-89.0)	0.95
Triglycerides Category, n (%)				0.29
<150 mg/dL	90 (9.8%)	751 (10.3%)	841 (10.3%)	
150 to <200 mg/dL	251 (27.3%)	2133 (29.4%)	2384 (29.1%)	
≥200 mg/dL	579 (62.9%)	4371 (60.2%)	4950 (60.5%)	

Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

Time to Coronary Revascularization



Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.

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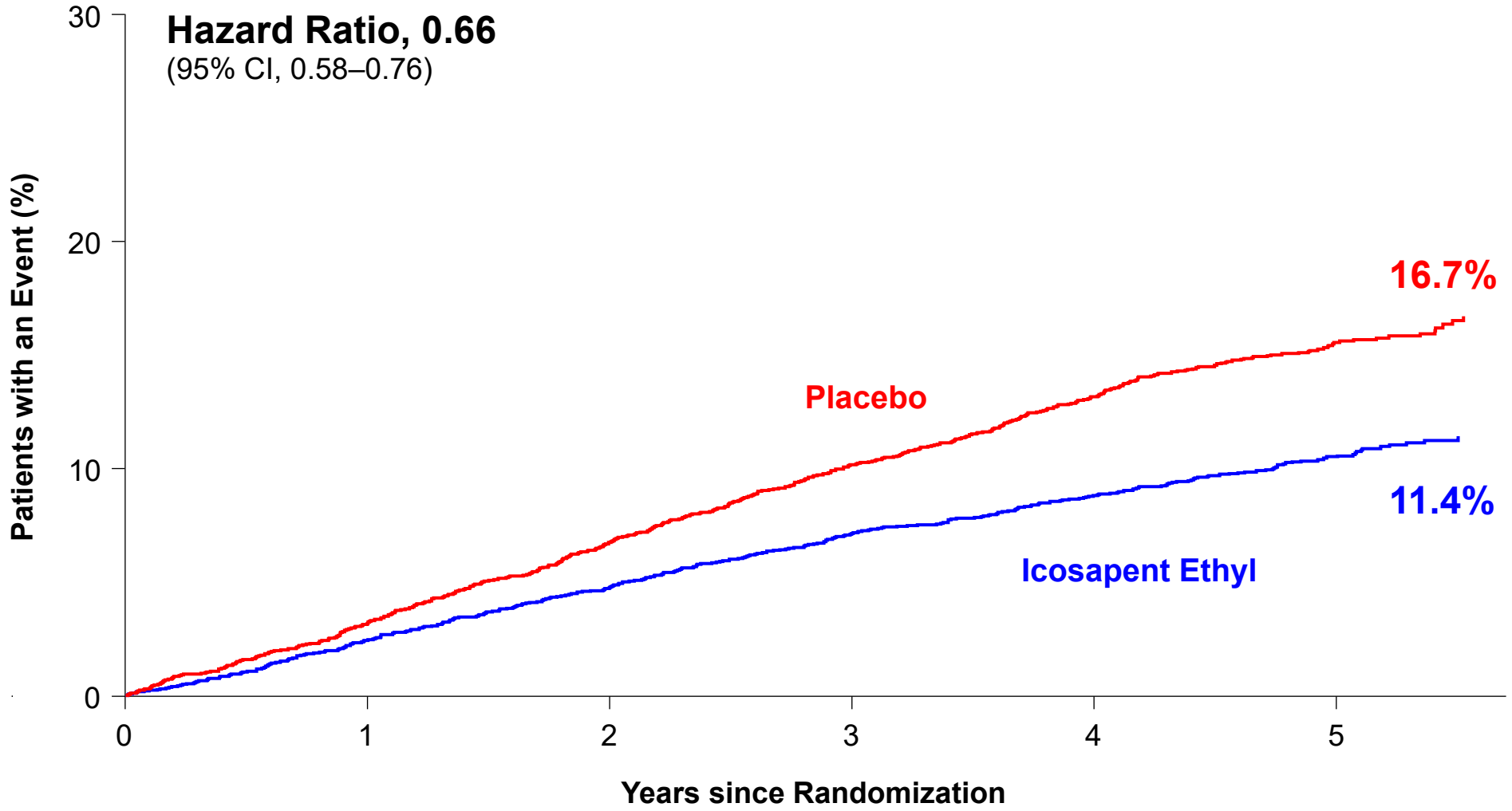

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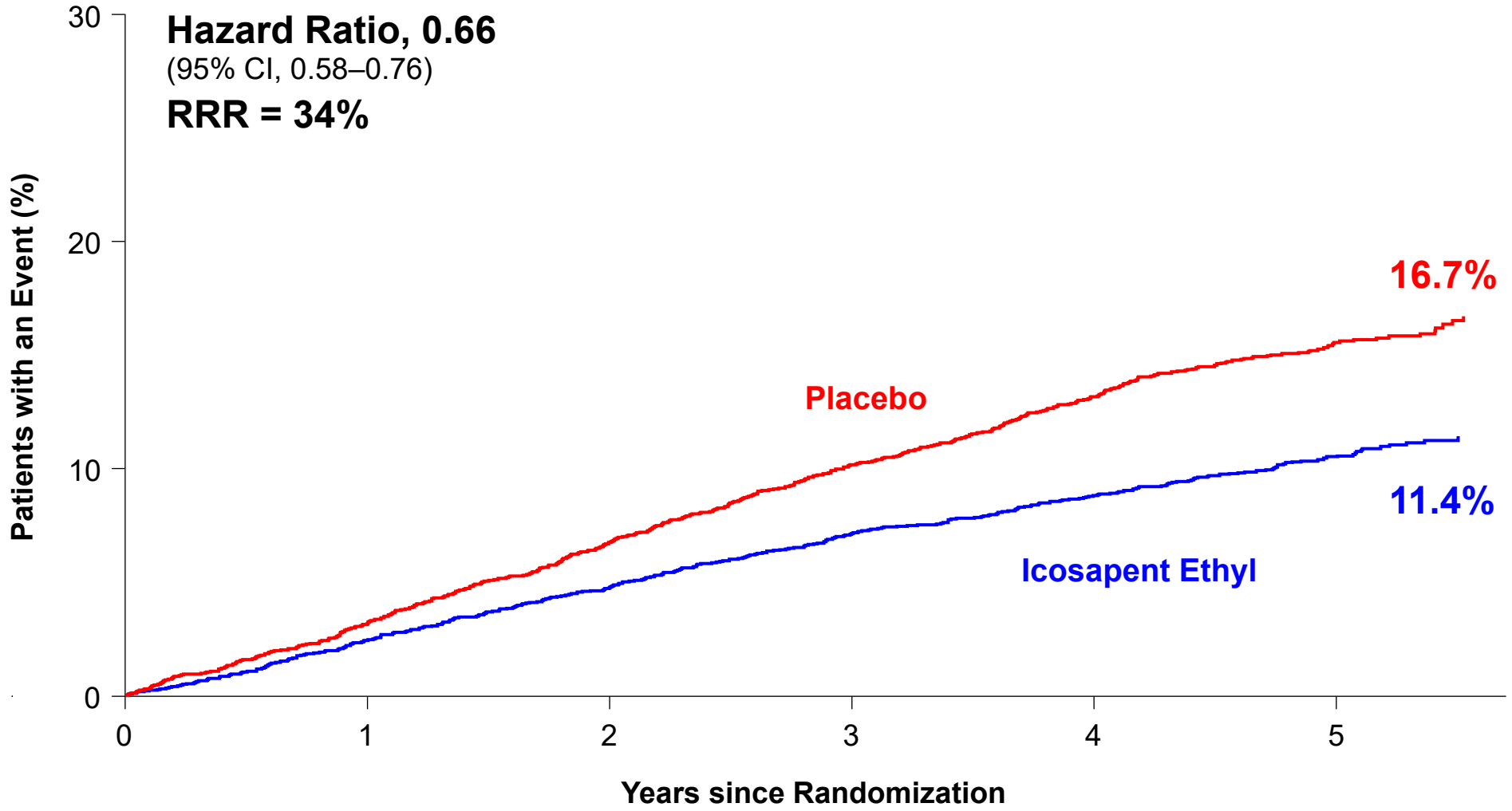

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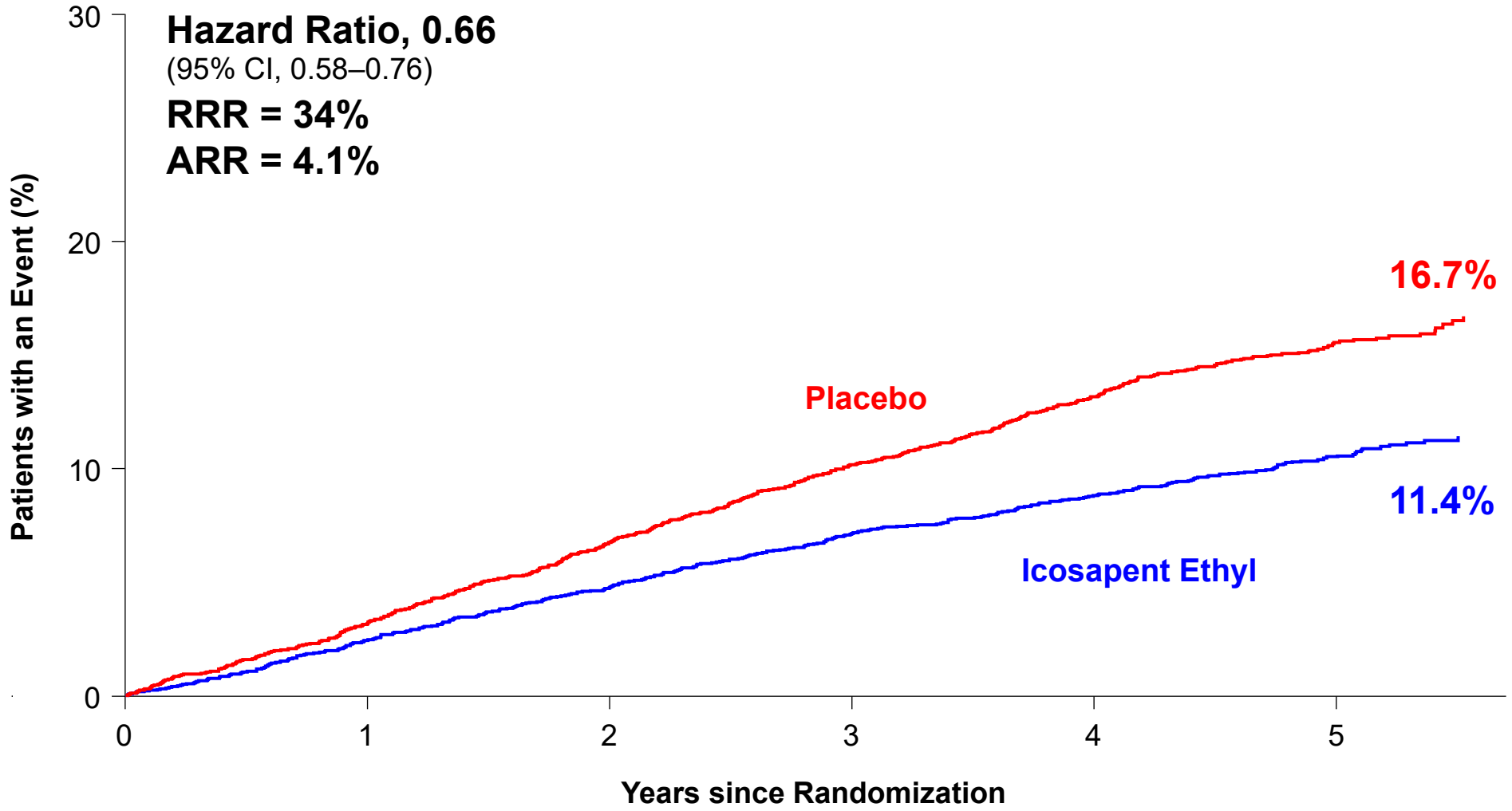

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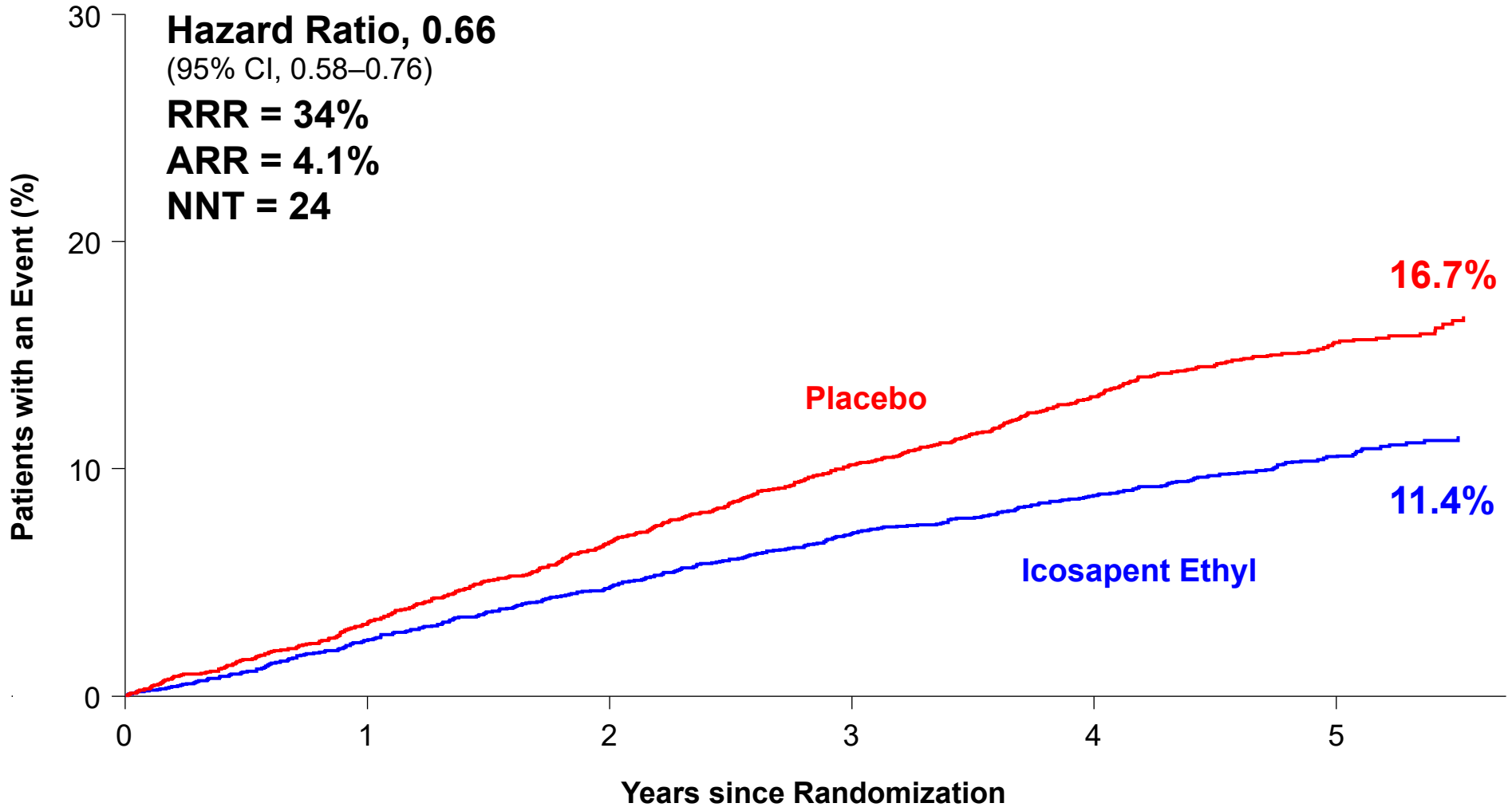

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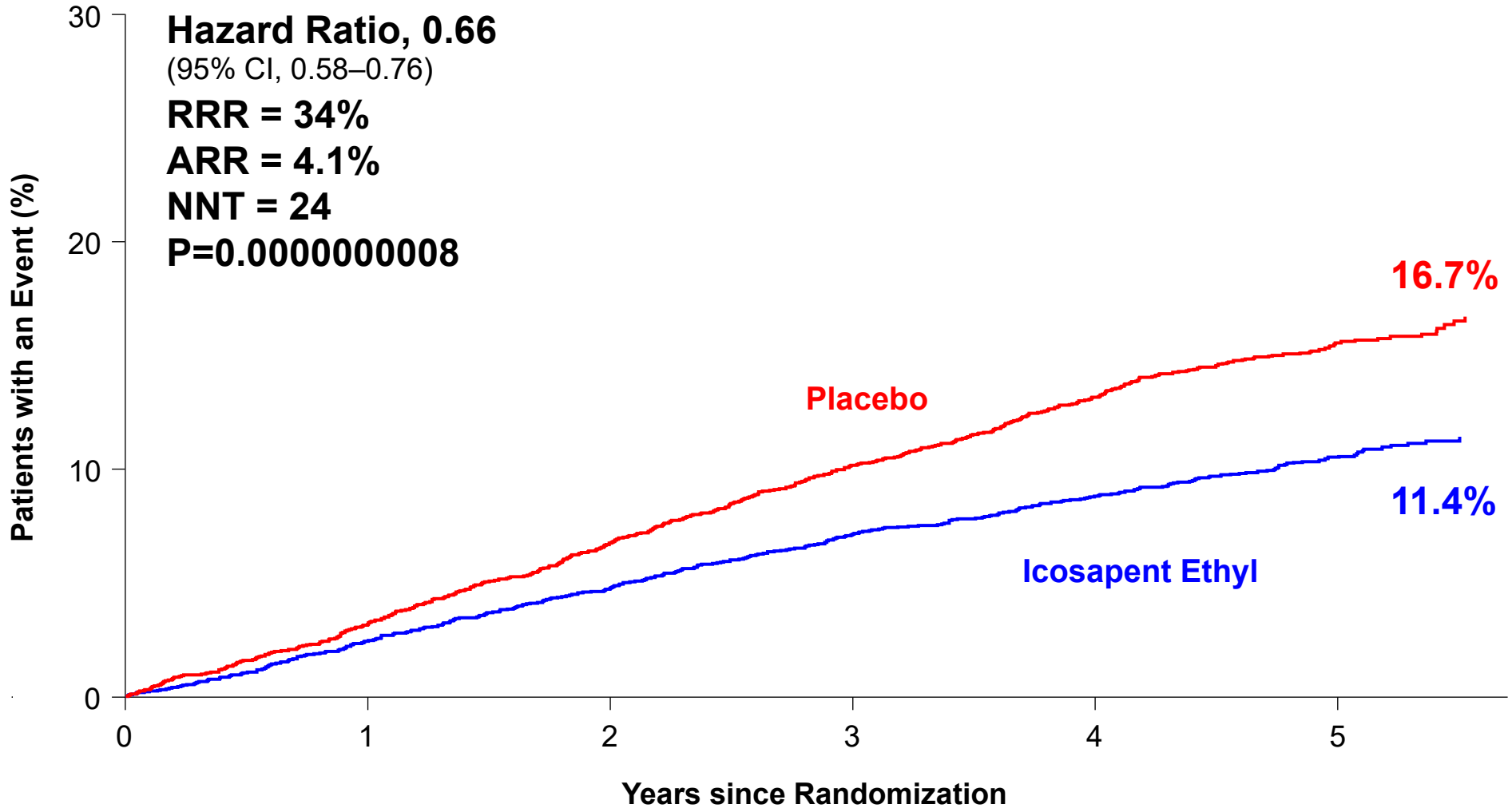

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First Coronary Revascularization Endpoints

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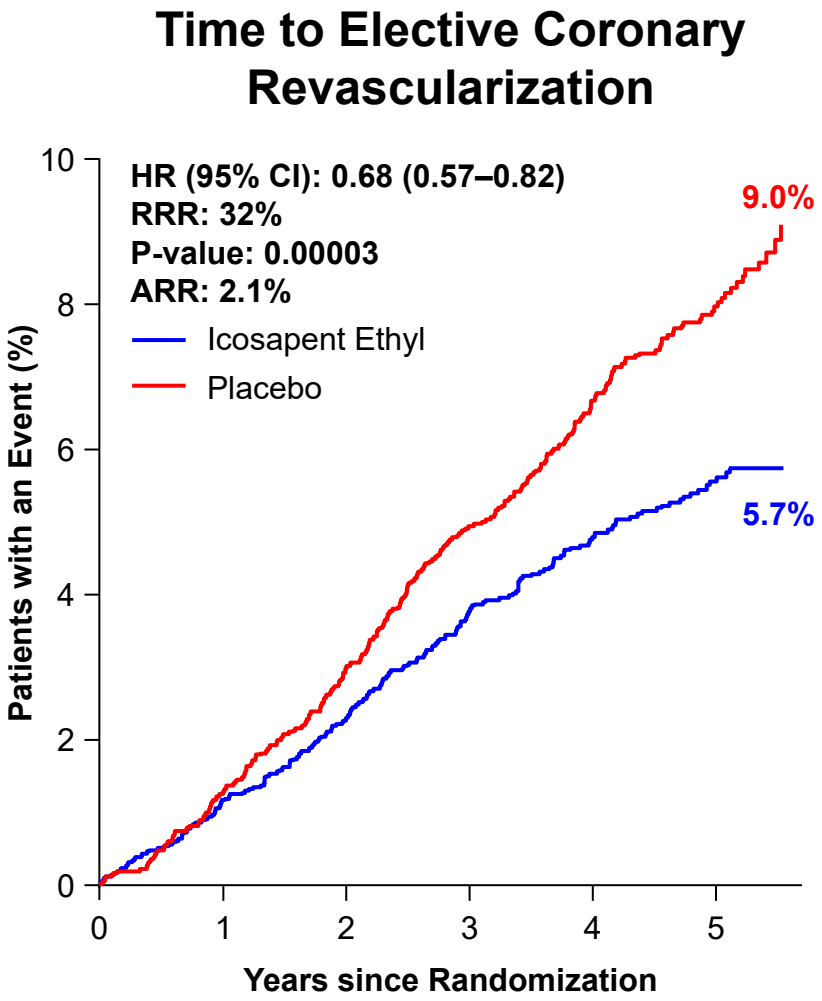
First Coronary Revascularization Endpoints: Icosapent Ethyl vs. Placebo

						Rate per 1000 Patient-Years	
	Icosapent Ethyl N=4089	Placebo N=4090	HR (95% CI)	Relative Risk Reduction	P-value	Icosapent Ethyl	Placebo
Coronary Revascularization	376 (9.2%)	544 (13.3%)	0.66 (0.58–0.76)	34%	<0.0001	22.5	33.7
Emergent or Urgent Revascularization	216 (5.3%)	321 (7.8%)	0.65 (0.55–0.78)	35%	<0.0001	12.6	19.3
Emergent Revascularization	41 (1.0%)	65 (1.6%)	0.62 (0.42–0.92)	38%	0.016	2.3	3.8
Urgent Revascularization	181 (4.4%)	268 (6.6%)	0.66 (0.54–0.79)	34%	<0.0001	10.5	16.0
Elective Revascularization	194 (4.7%)	278 (6.8%)	0.68 (0.57–0.82)	32%	<0.0001	11.3	16.5
Salvage Revascularization	0 (0.0%)	2 (0.0%)	0.00 (0.00–0.00)	--	0.16	0.0	0.1

Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

Time to Elective, Emergent, and Urgent Revascularization Events



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Time to Elective, Emergent, and Urgent Revascularization Events

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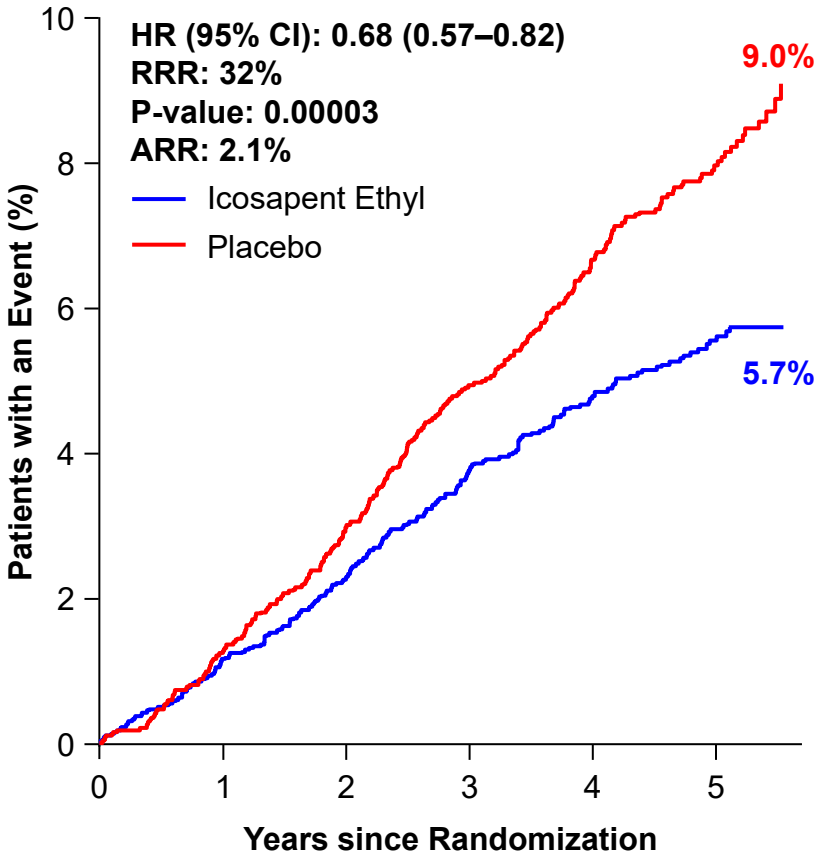
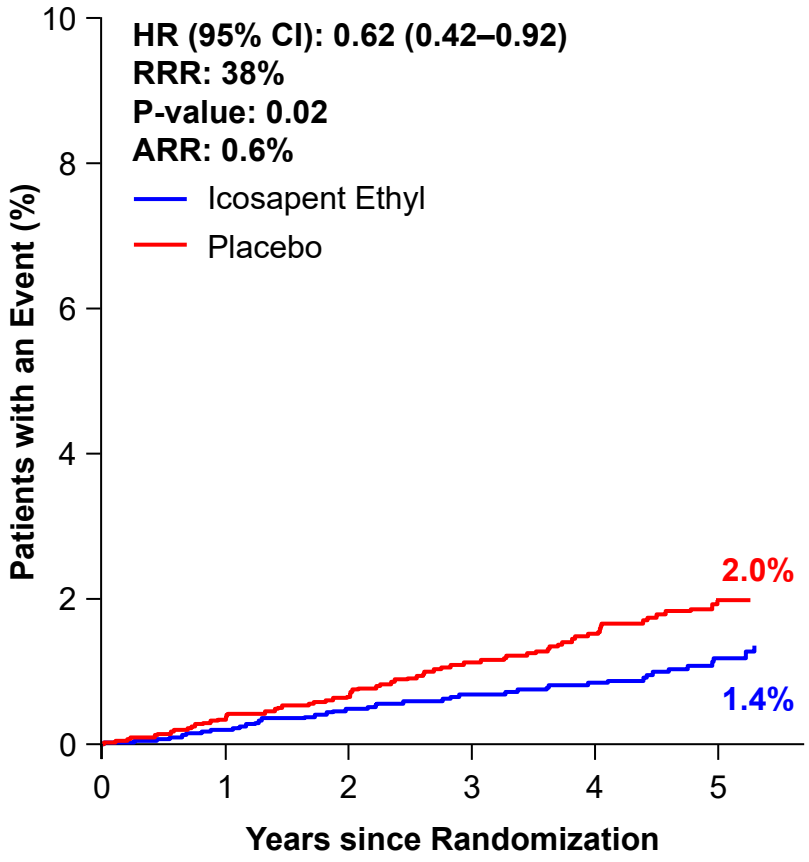
Time to Elective Coronary Revascularization



Time to Emergent Coronary Revascularization



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Time to Emergent Coronary Revascularization ARR is based on the observed event rates of 1.0% for IPE and 1.6% for Placebo.

Time to Elective, Emergent, and Urgent Revascularization Events

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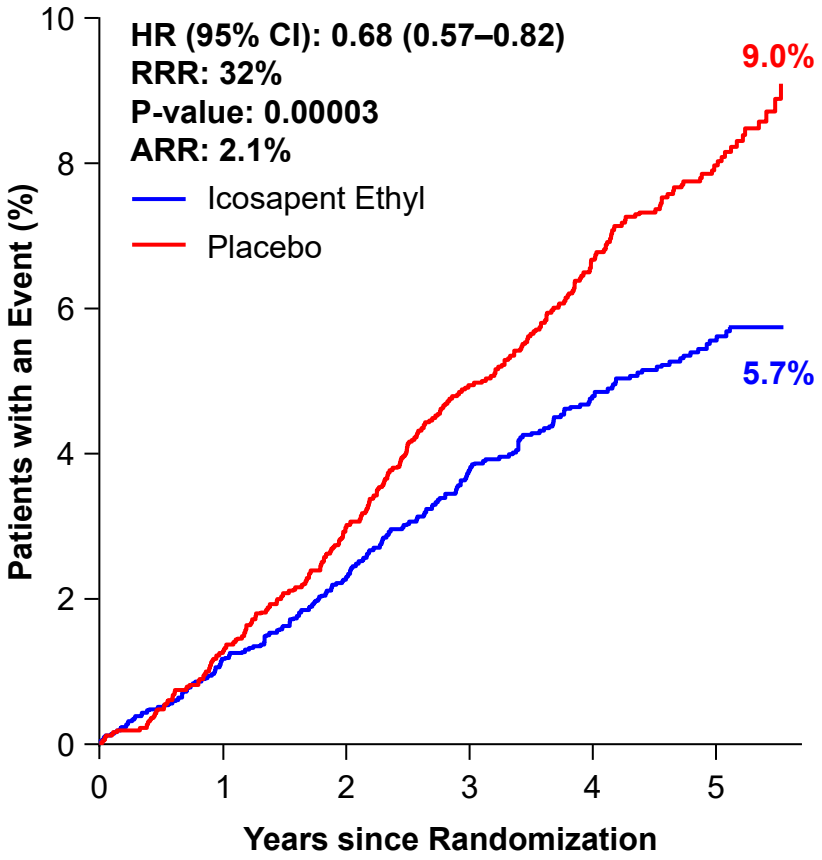
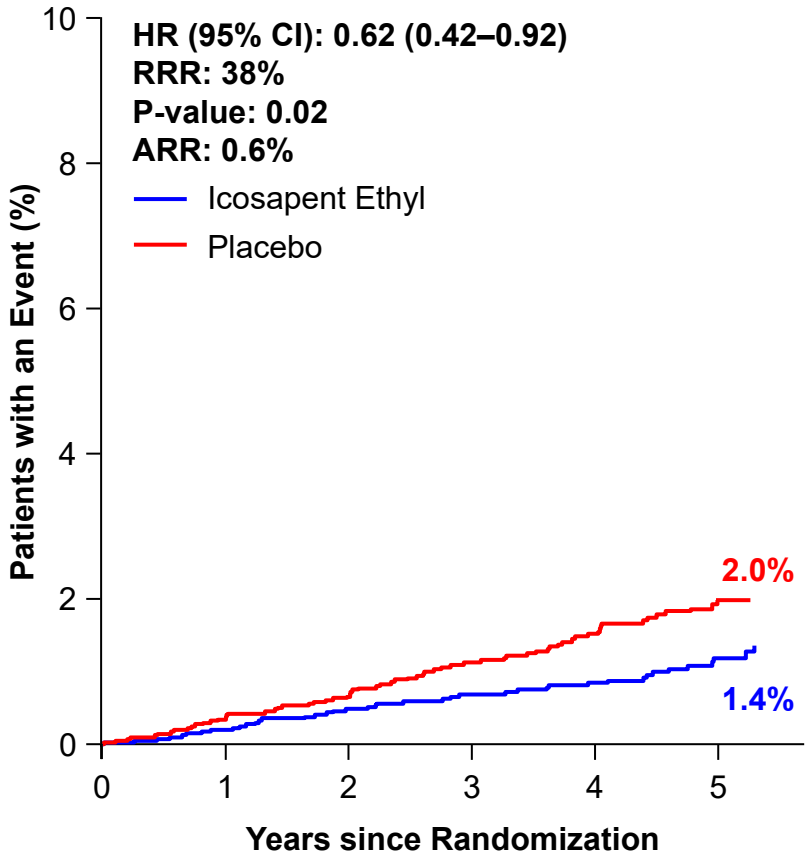
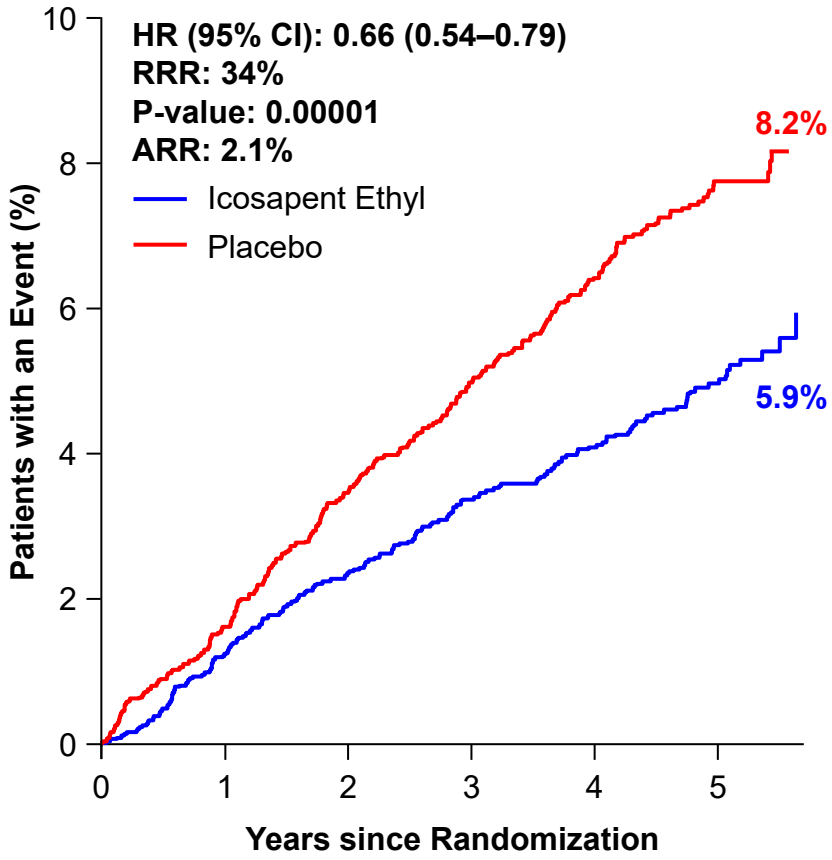
Time to Elective Coronary Revascularization



Time to Emergent Coronary Revascularization



Time to Urgent Coronary Revascularization



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Time to Urgent Coronary Revascularization ARR is based on the observed rates of 4.4% for IPE and 6.6% for Placebo.

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Time to PCI and CABG

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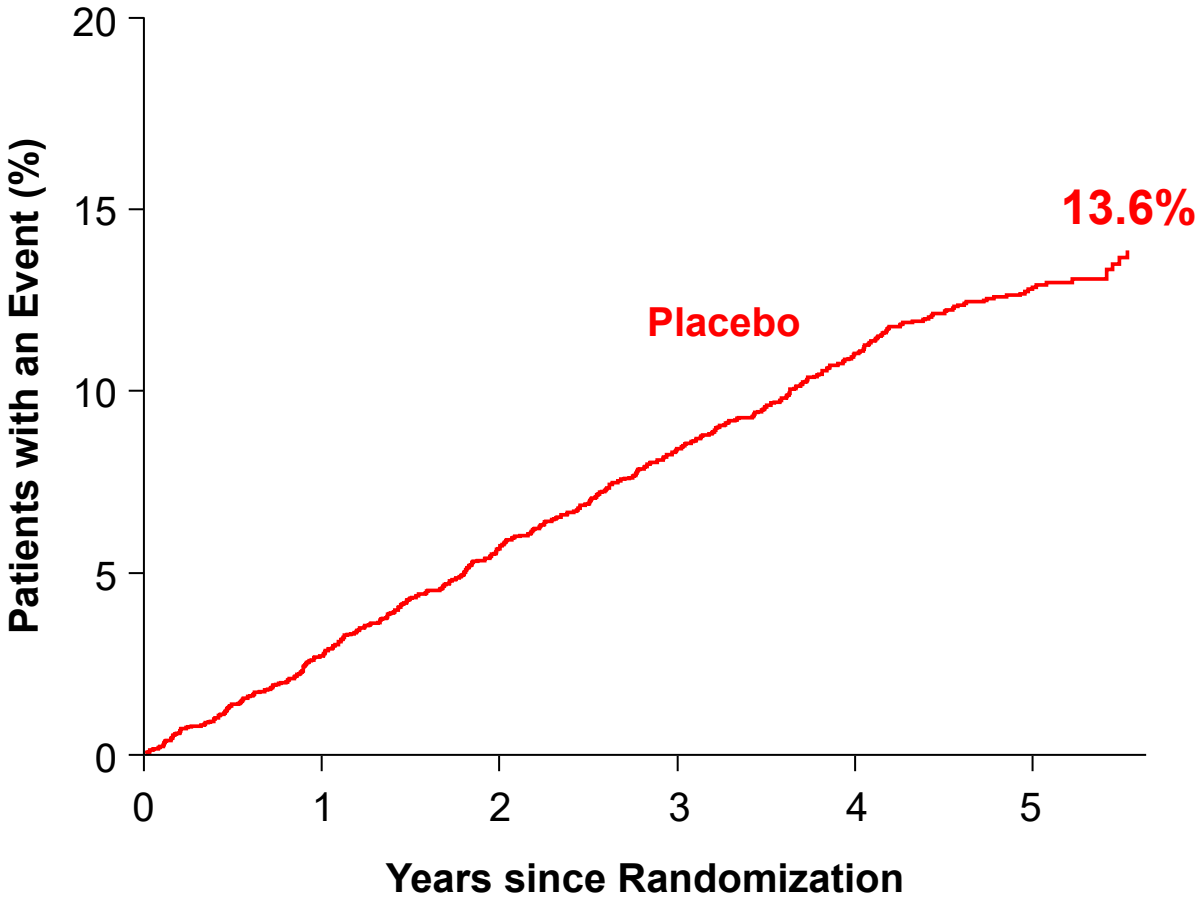
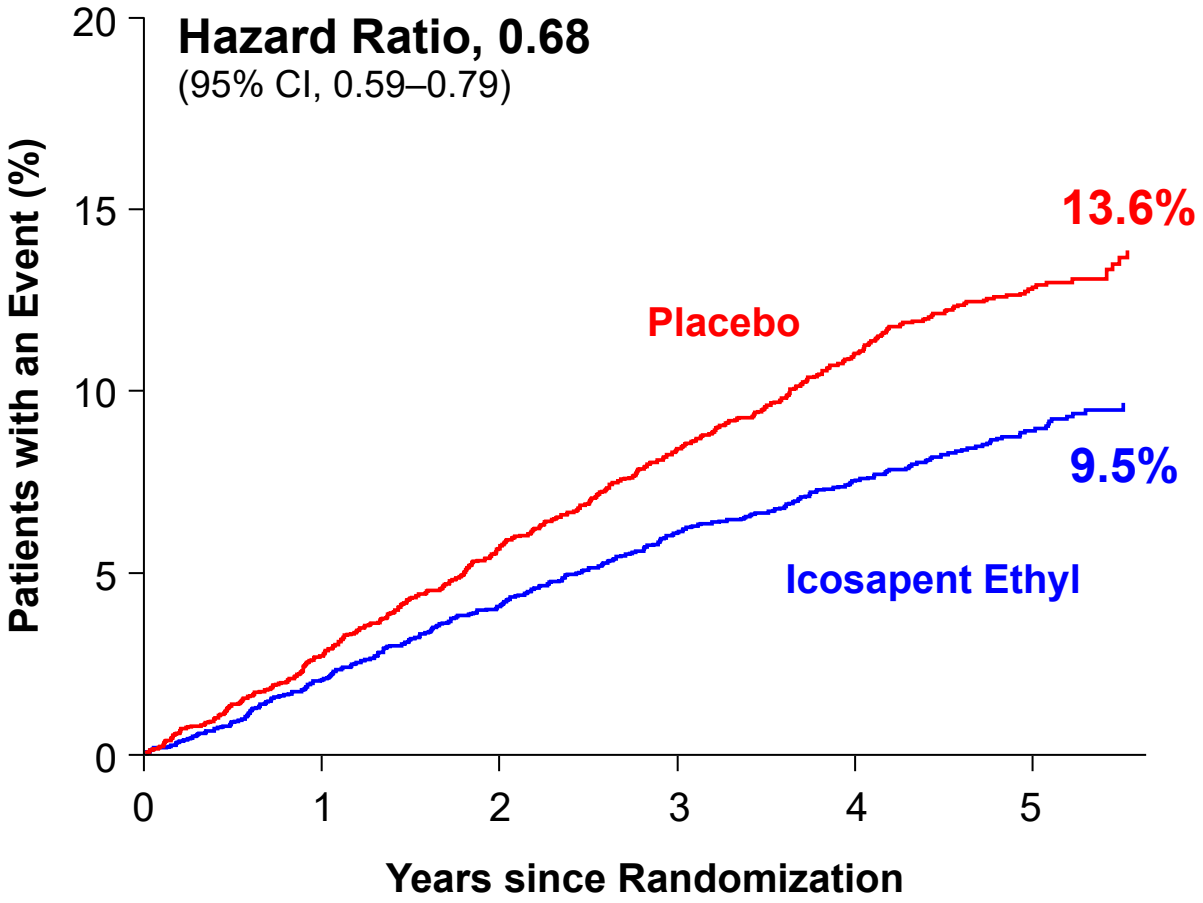
Time to Percutaneous Coronary Intervention



Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual). Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.

Time to PCI and CABG

Time to Percutaneous Coronary Intervention



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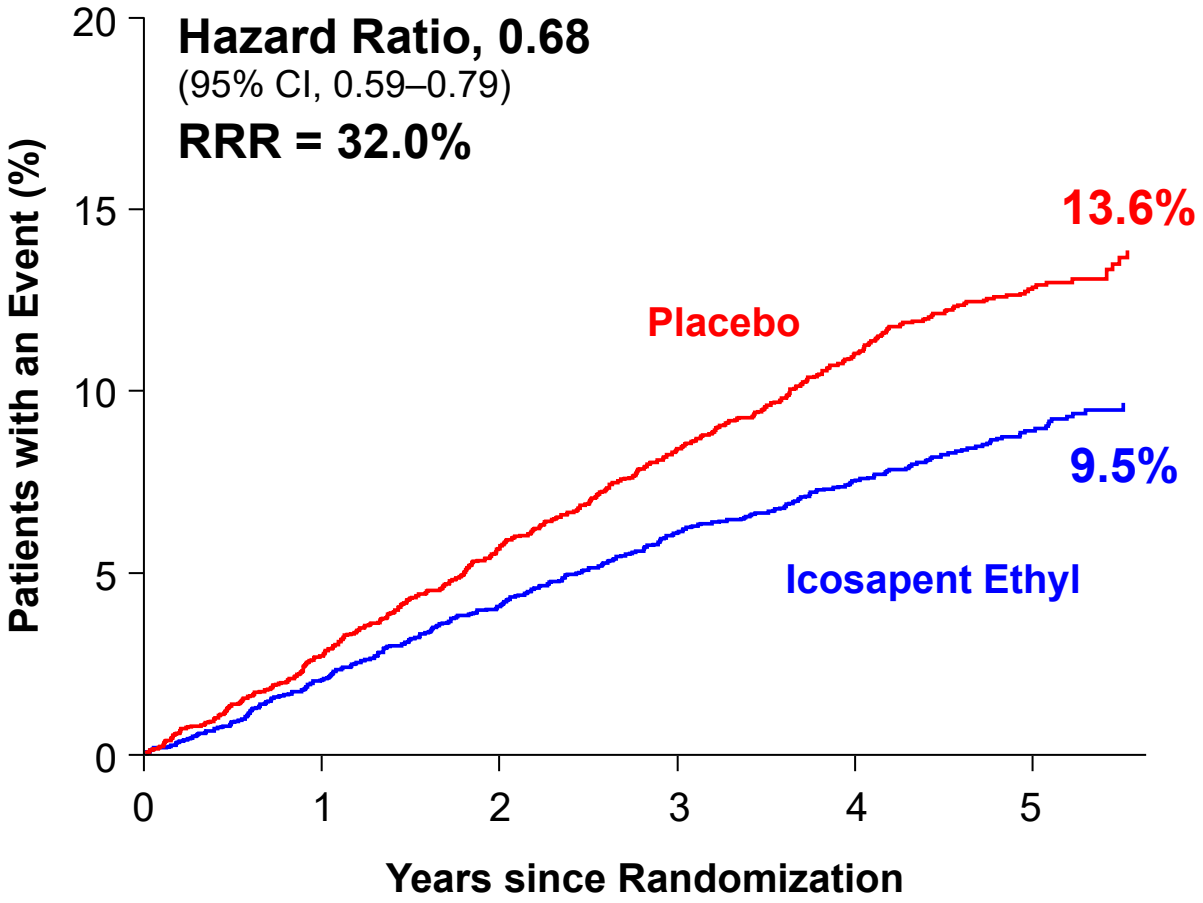

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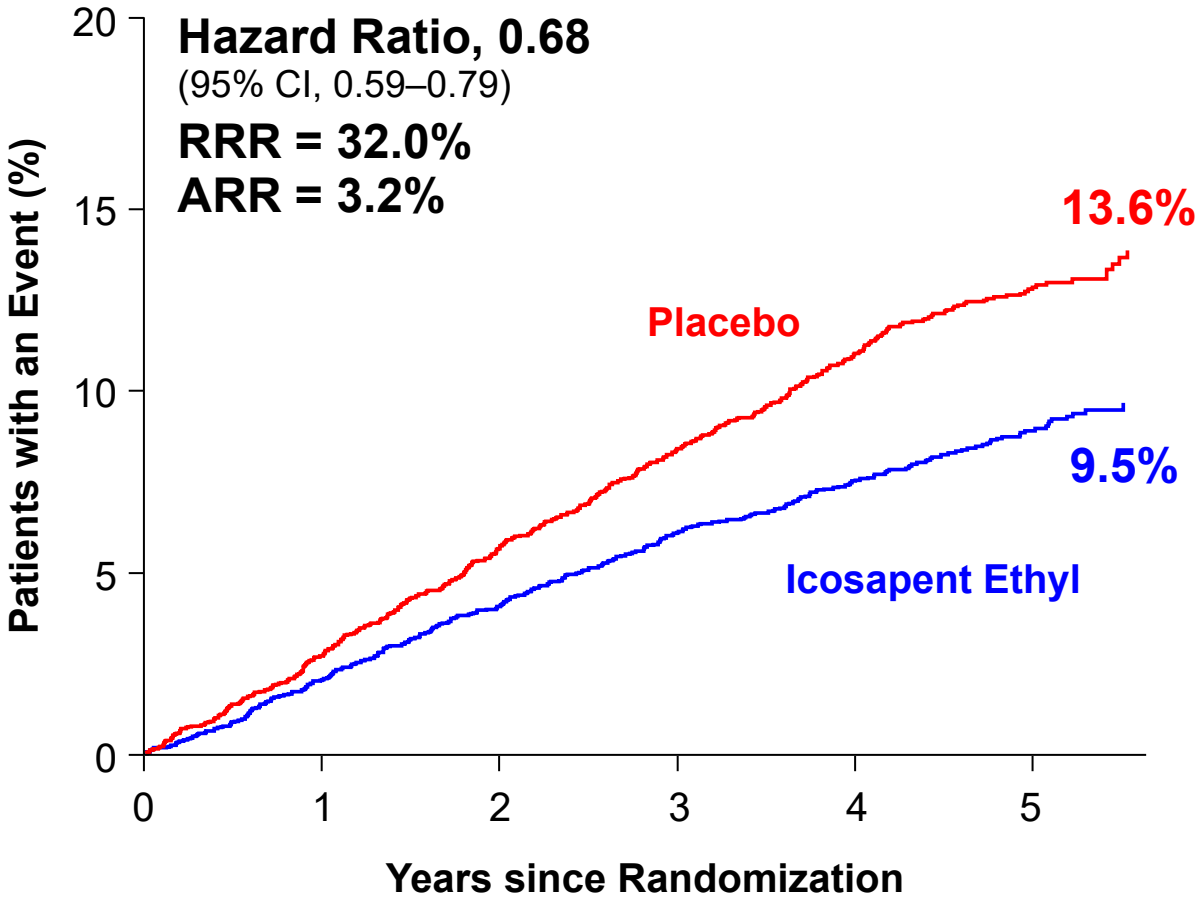

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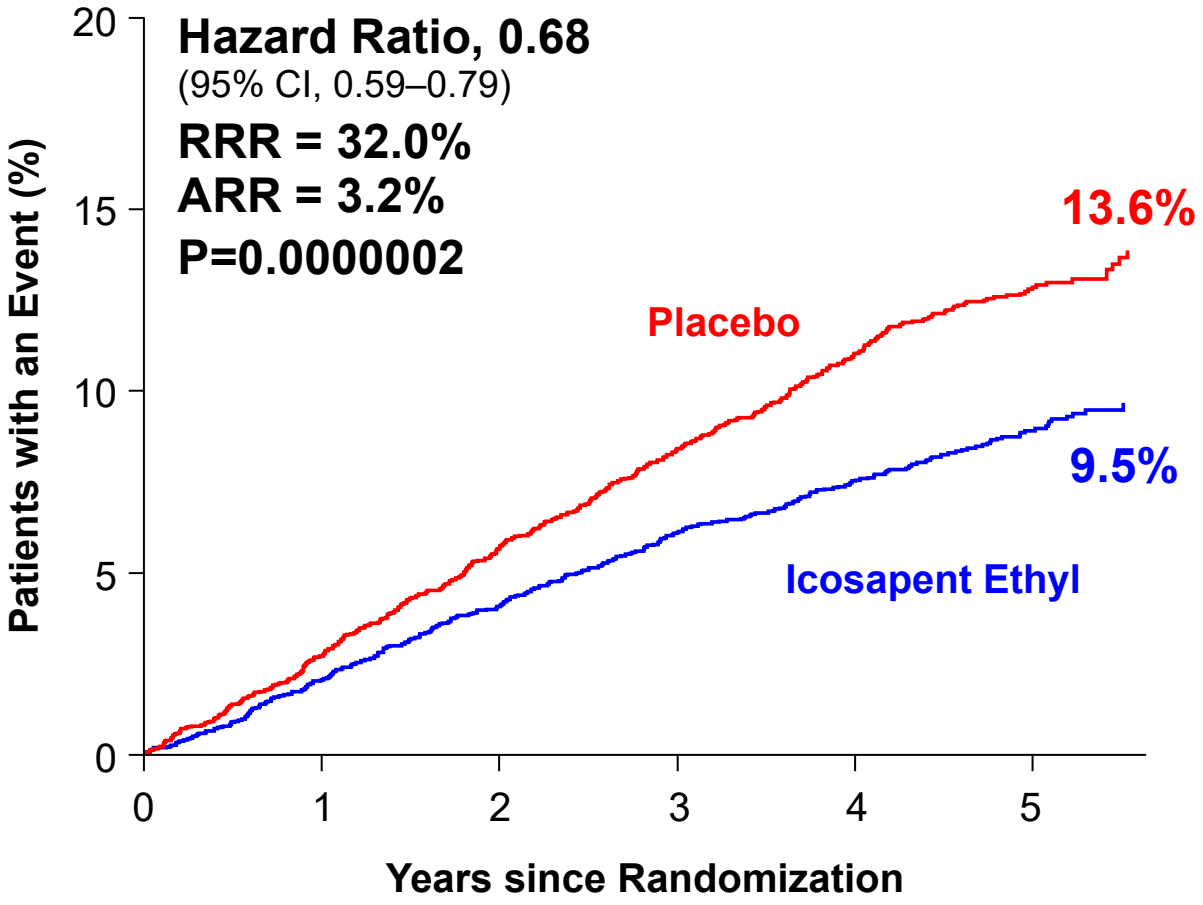

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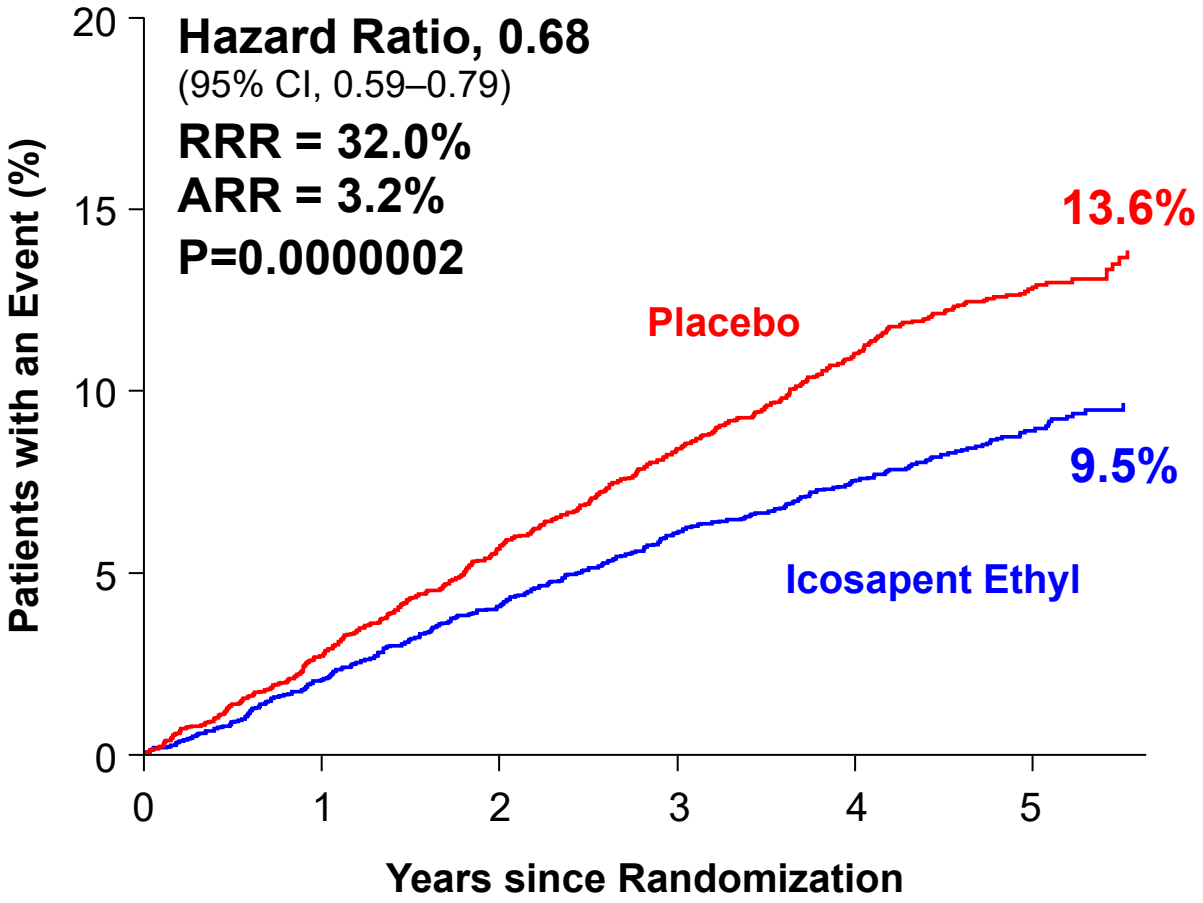
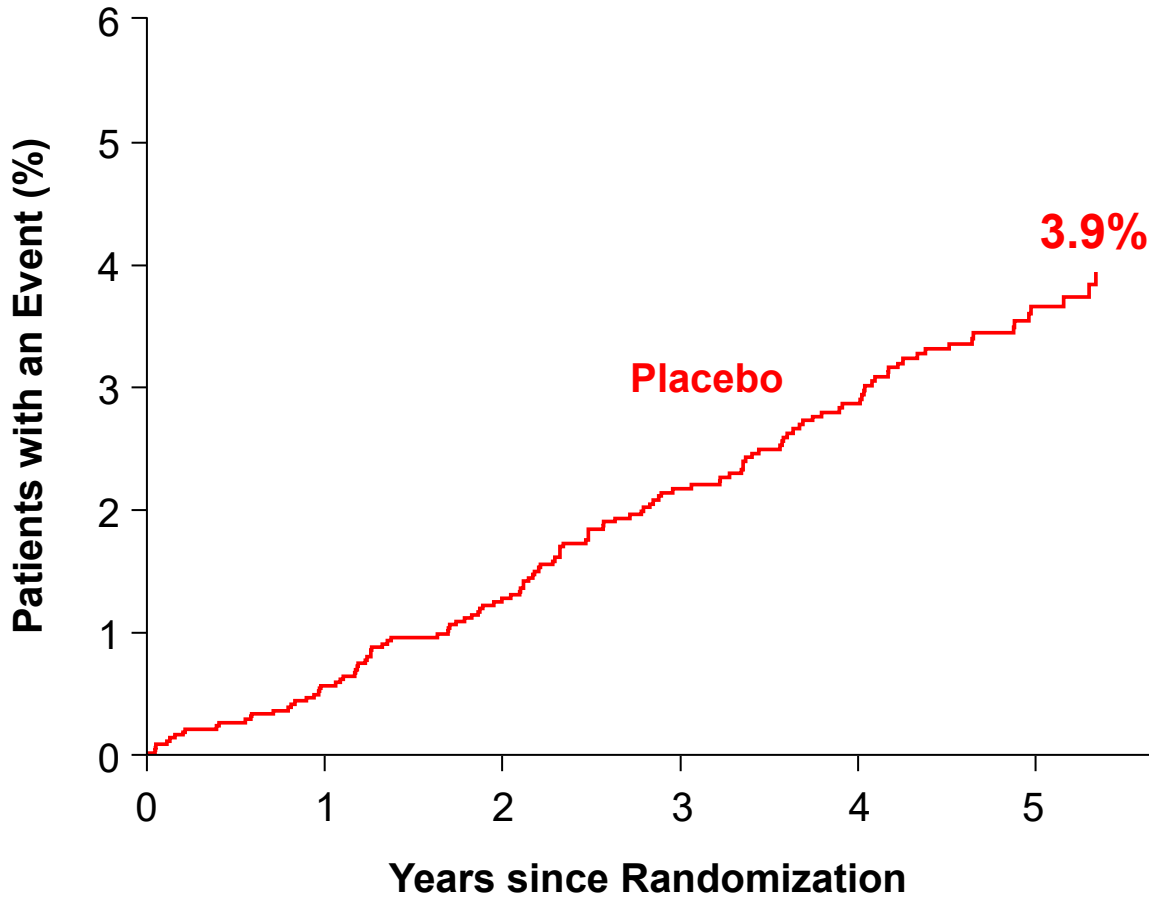


Time to Coronary Artery Bypass Graft



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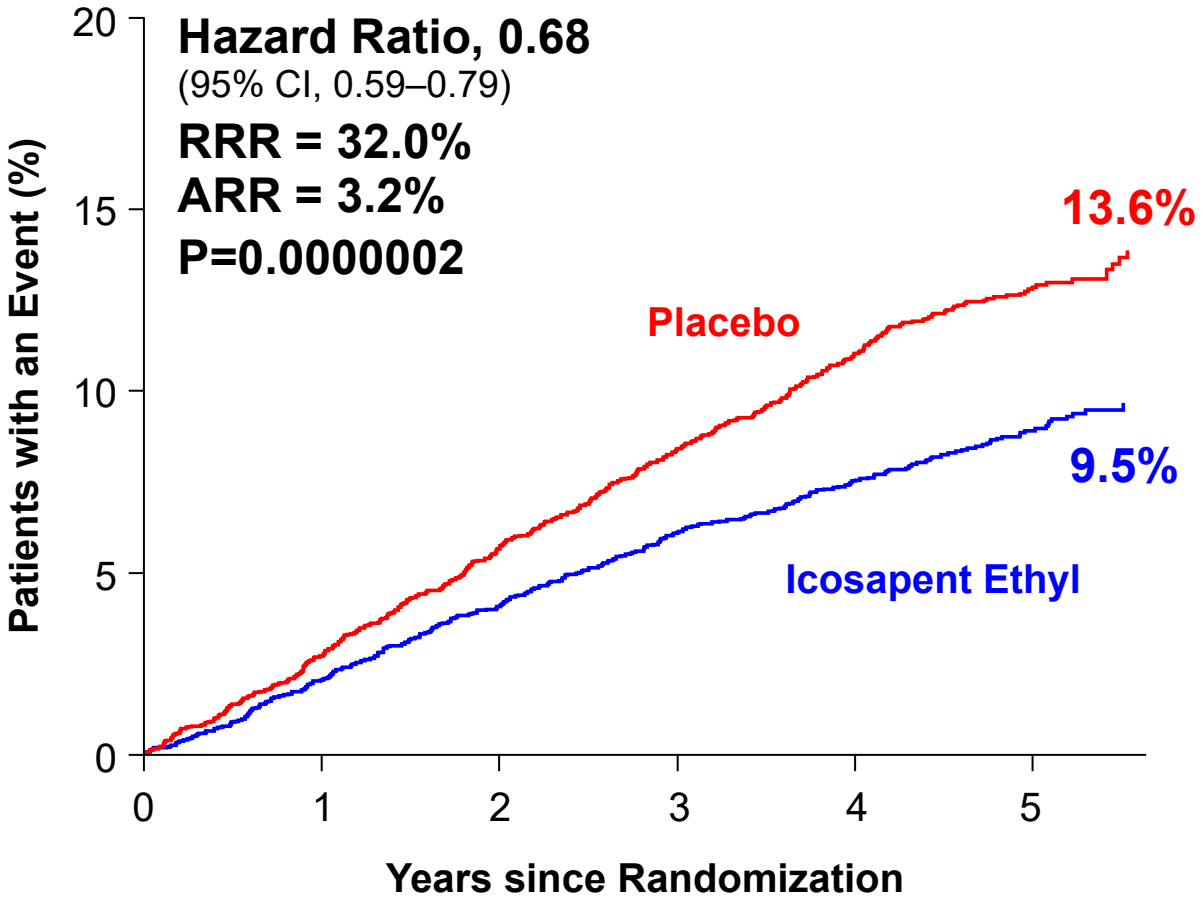

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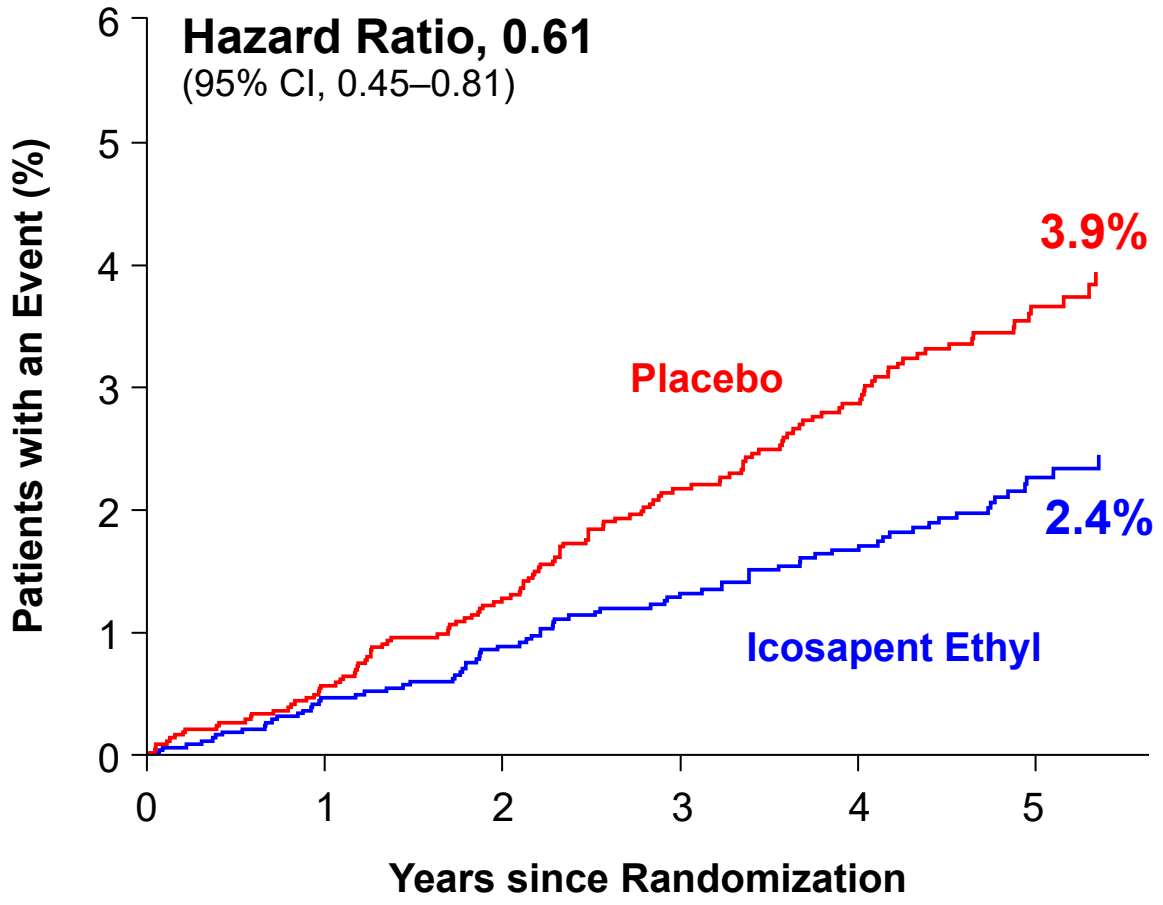

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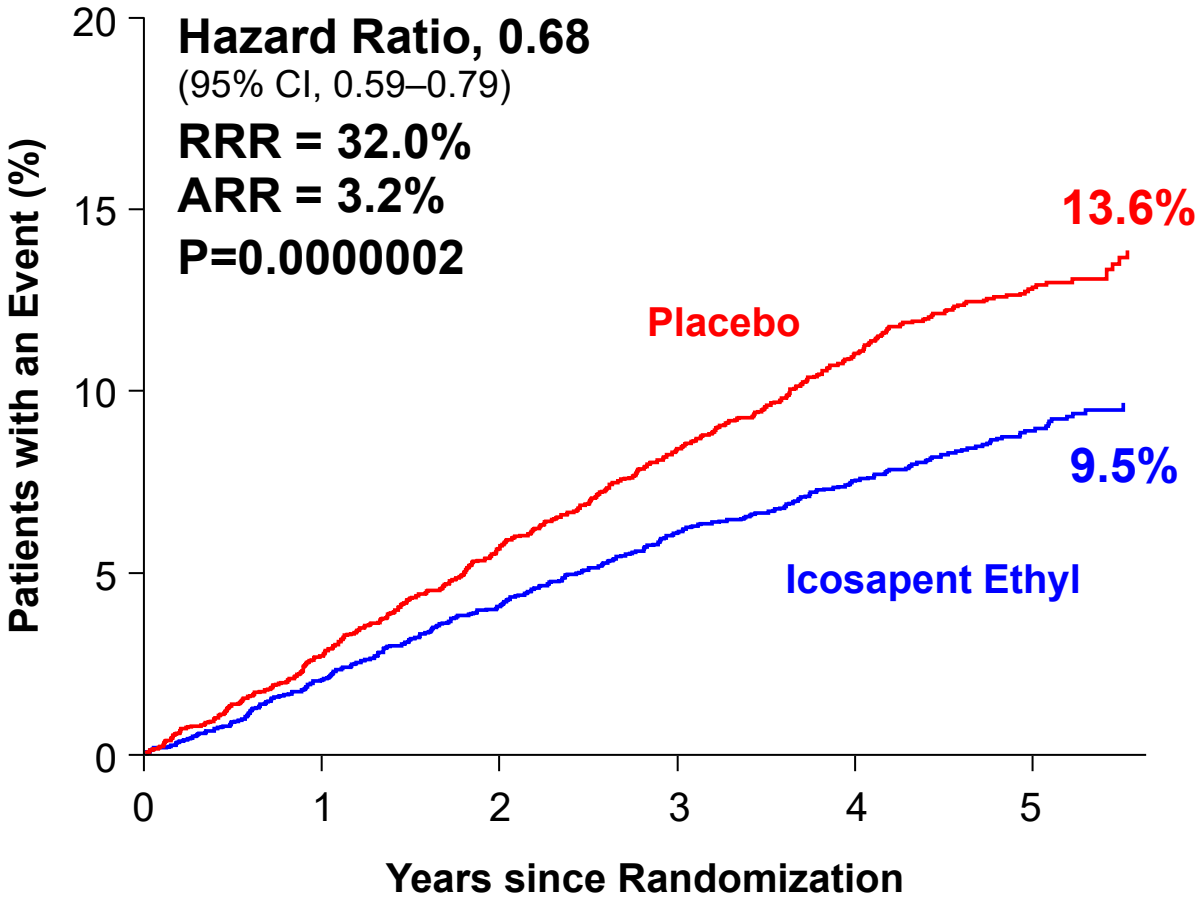

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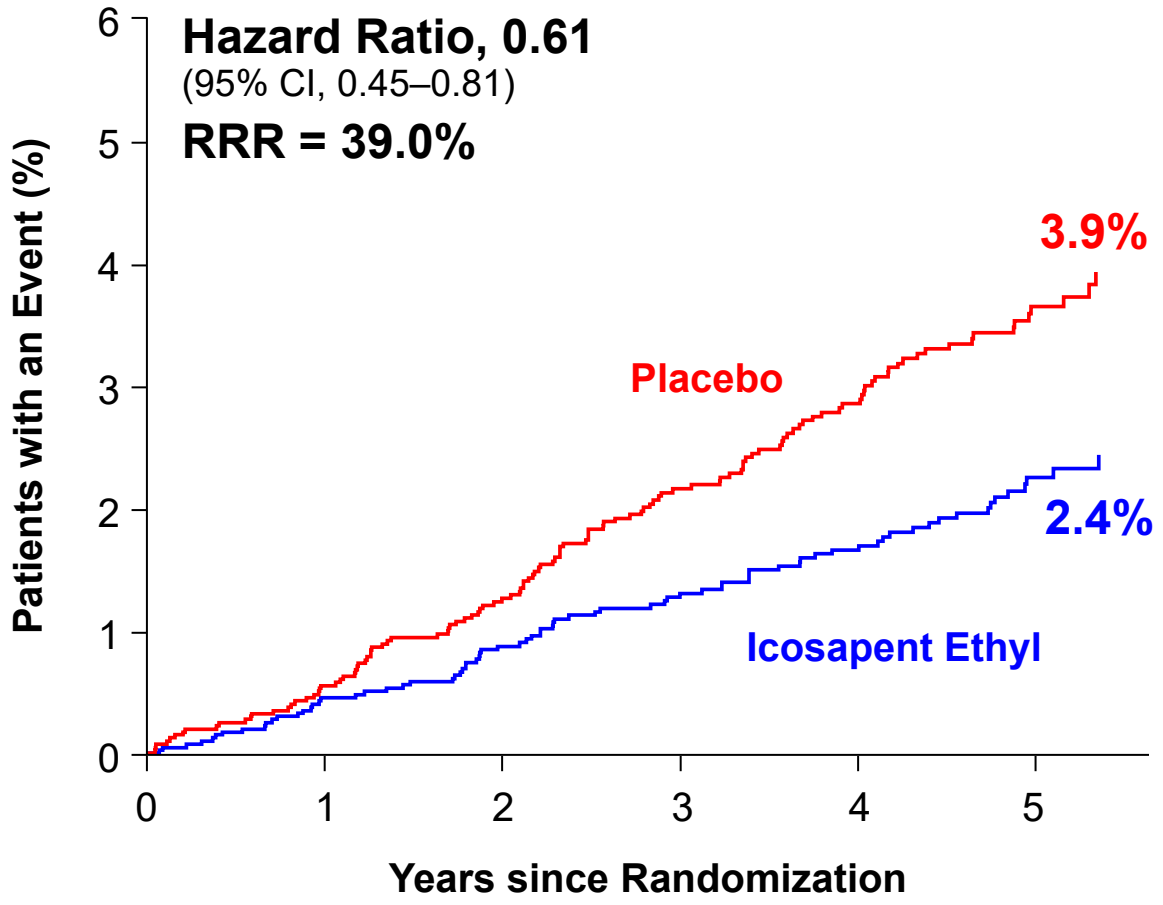

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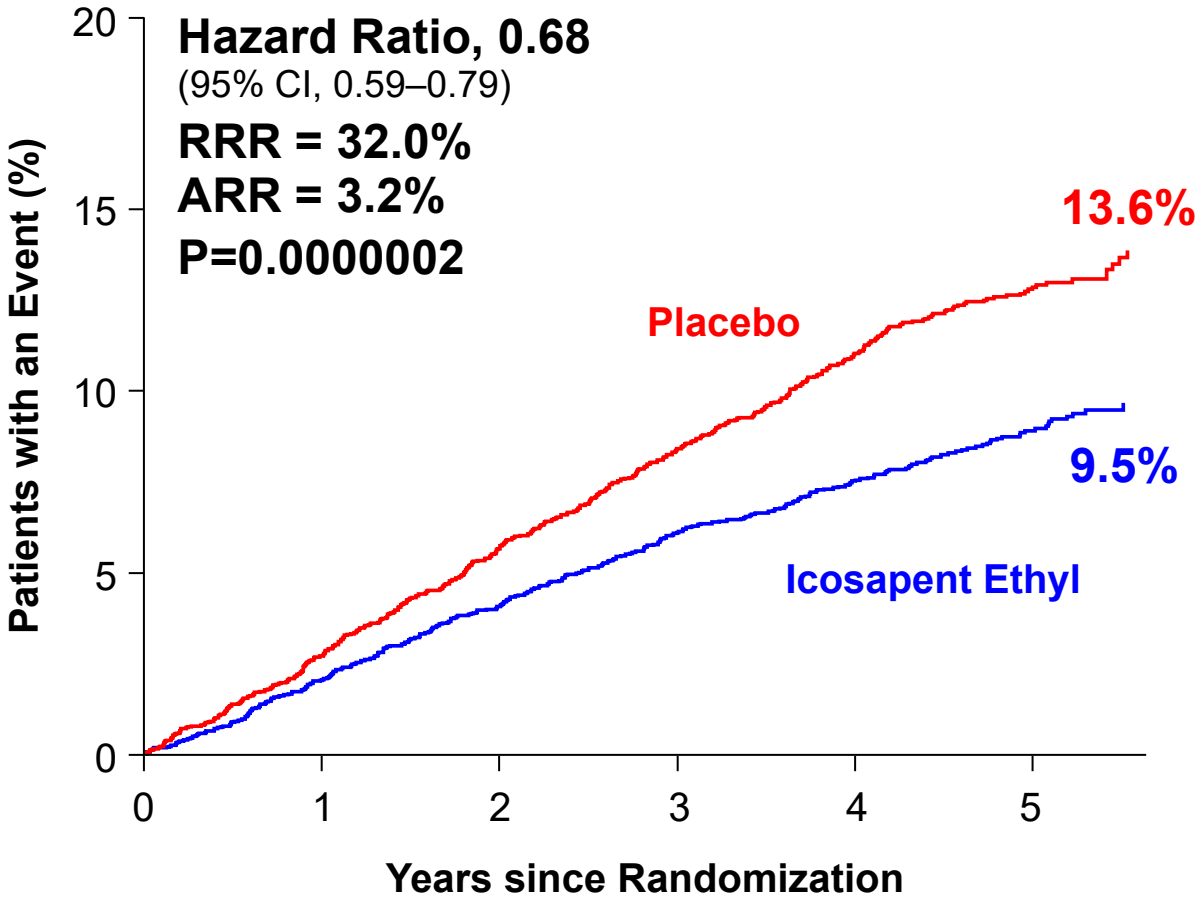
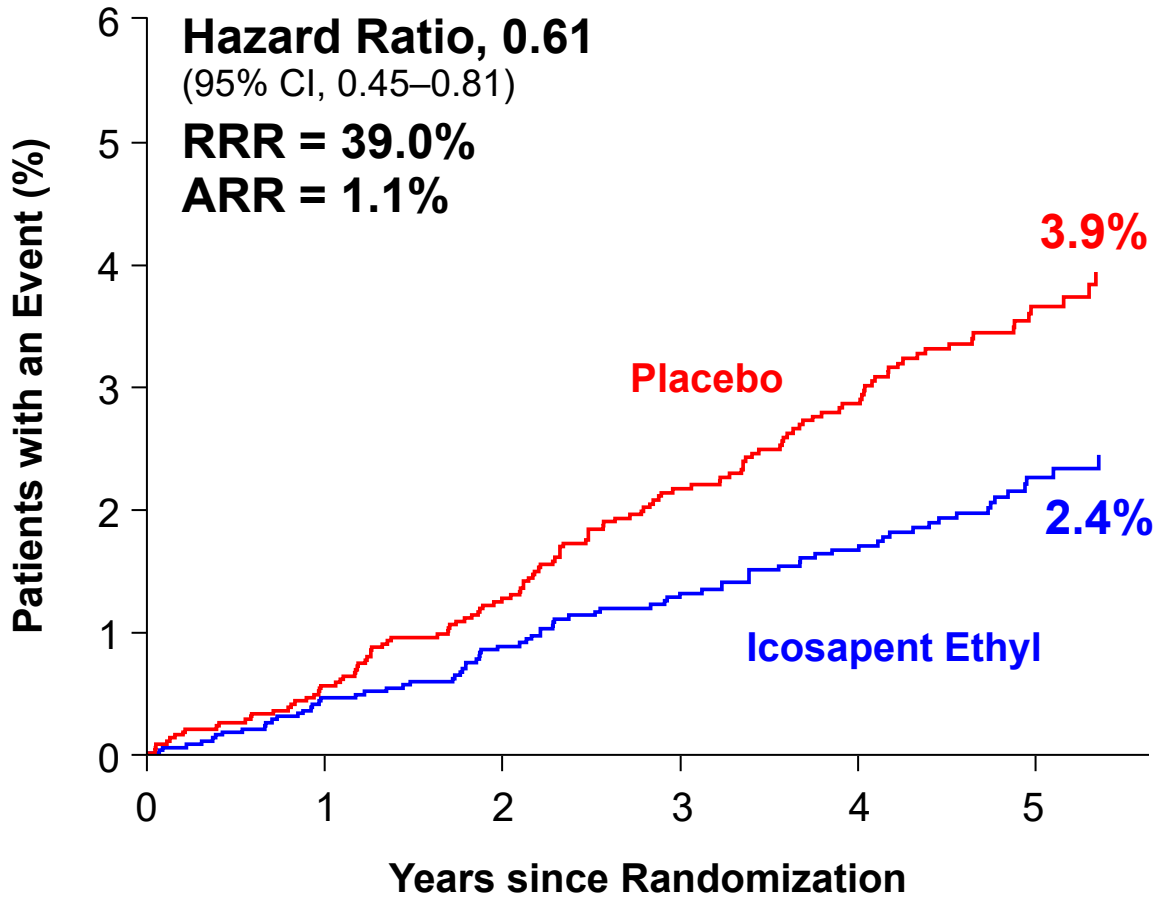
Time to Percutaneous Coronary Intervention



Time to Coronary Artery Bypass Graft



Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.
Time to PCI ARR is based on the observed event rates of 7.7% for IPE and 10.9% for Placebo.
Time to CABG ARR is based on the observed event rates of 2.9% for IPE and 3.0% for Placebo.

Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

Time to PCI and CABG

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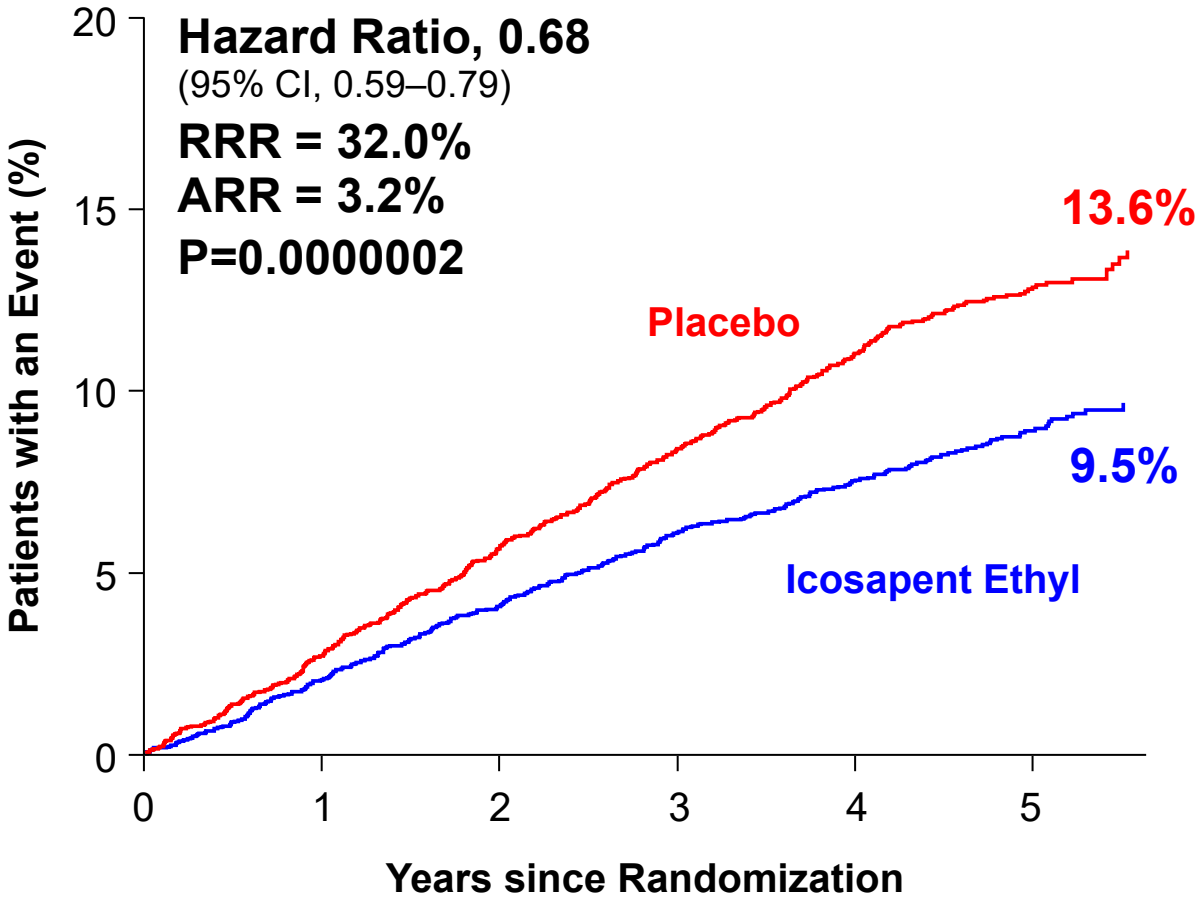
Time to Percutaneous Coronary Intervention



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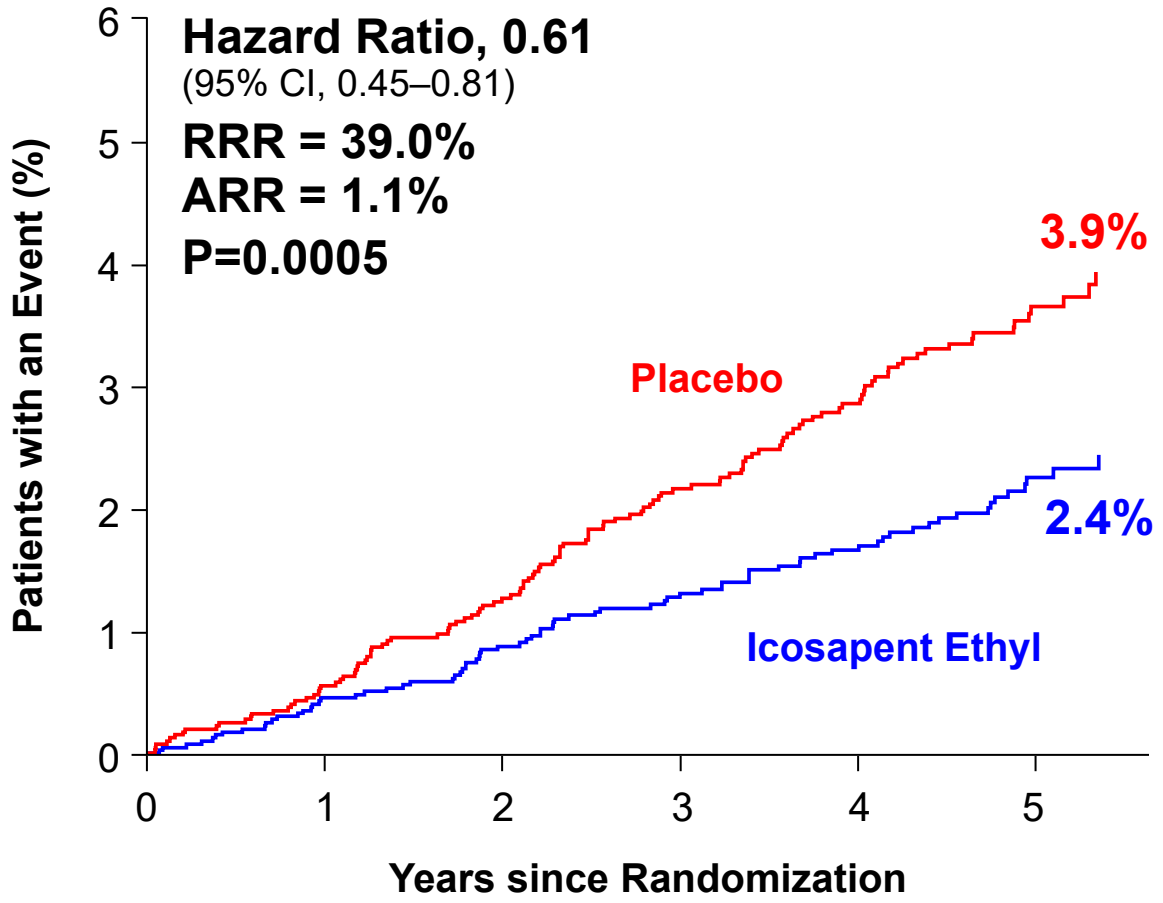

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Independent Predictors of Revasc

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Stepwise Selected Covariate			
Covariates	**Hazard Ratio (95% CI)[1]**	**Relative Risk Reduction**	**P-value[1]**
Treatment: Icosapent Ethyl vs Placebo	0.64 (0.56-0.73)	36%	<0.0001
Prior PCI: Yes vs No	2.24 (1.92-2.62)	---	<0.0001
Sex: Male vs Female	1.53 (1.29-1.81)	---	<0.0001
Baseline Diabetes: Yes vs No	1.46 (1.26-1.68)	---	<0.0001
Baseline TG: 1 mmol/L (88.57 mg/dL) increase	1.14 (1.07-1.22)	---	<0.0001
Baseline hsCRP: 1 mg/L increase	1.11 (1.02-1.21)	---	0.0125

Note: Identified significant covariates are from a stepwise selection process using the Cox proportional hazard model, with 0.05 and 0.1 p-value for a covariate required for entry and to stay in the model, respectively. Variables considered for stepwise selection: Age (<65, ≥65 Years), Sex (Female, Male), Race (White, Non-White), Diabetes (Yes, No), Smoking Status (Current/Former, Never), Hypertension (Yes, No), BMI Category (<25 kg/m^2, ≥25 to <30 kg/m^2, ≥30 kg/m^2), Baseline LDL-C (derived), Baseline TG, Baseline HDL-C, Baseline hsCRP, Prior MI (Yes, No), Prior PCI (Yes, No), Prior CABG (Yes, No), Baseline statin intensity (Low, Moderate, High).
[1] Hazard ratio, 95% CI and p-value are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

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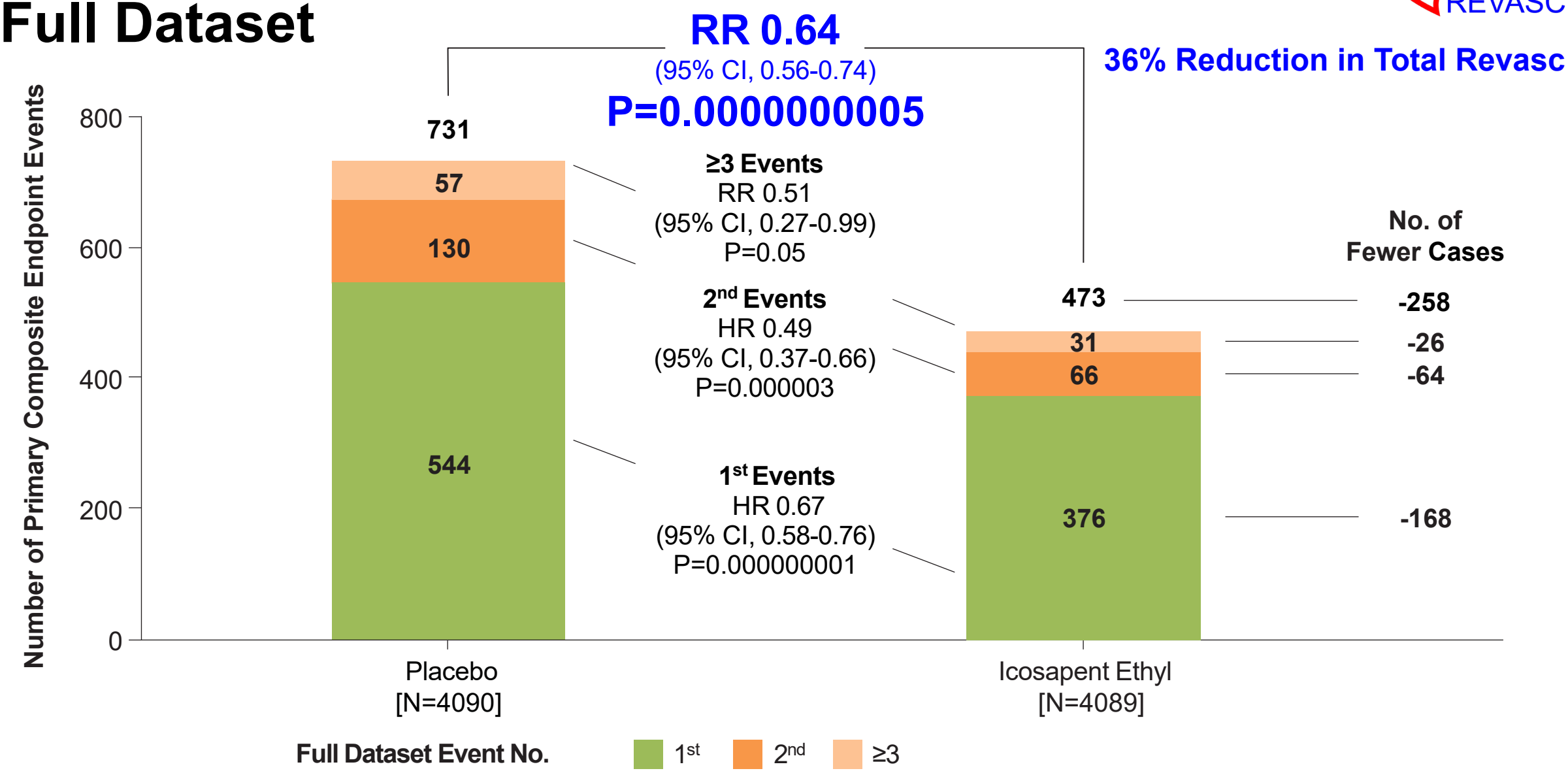
First and Subsequent Revasc Events

Full Dataset



Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

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

Limitations

Coronary revascularization as an endpoint can be considered subjective

Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

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- Each subtype of revascularization was similarly and statistically reduced
- Revascularization endpoints were adjudicated by an independent, blinded clinical endpoint committee evaluating data from a randomized, double-blind, placebo-controlled trial – therefore, no risk of bias

Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced first and total revascularization events by **34%** and **36%**, respectively

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These data highlight the substantial impact of icosapent ethyl on the underlying atherothrombotic burden in the at-risk **REDUCE-IT** population

Peterson BE, Bhatt DL, Steg PG, et al. SCAI 2020, Atlanta (virtual).

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

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Slides available for free download: www.scai.org