REDUCE IT: et après ?

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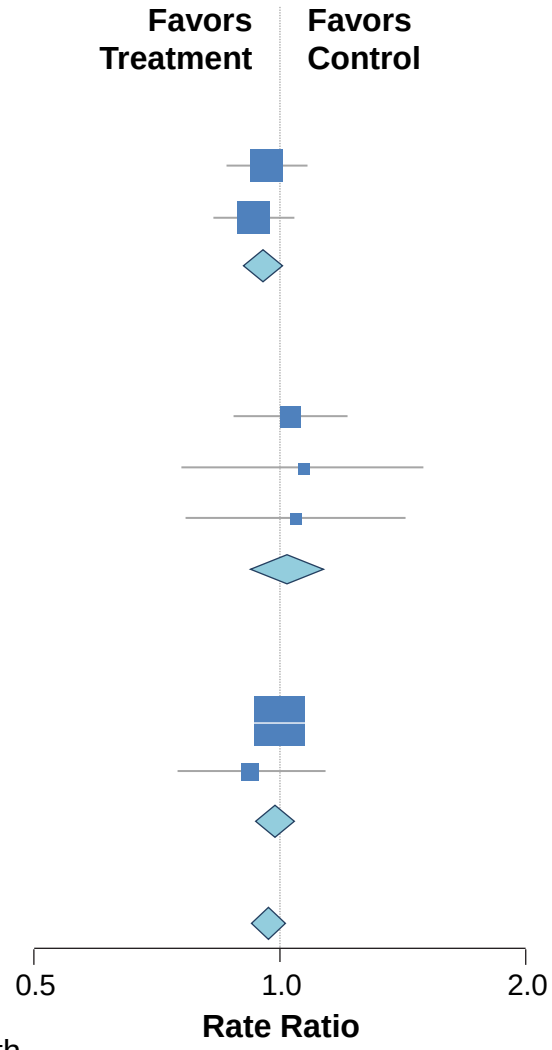
Disclosures

- **Research grants** : Amarin, Bayer, Sanofi, and Servier
- **Clinical Trials (Steering committee, CEC, DSMB)** : Amarin, AstraZeneca, Bayer, Bristol-Myers Squibb, Idorsia, Novartis, Pfizer, Sanofi, Servier
- **Consulting or speaking**: Amarin, Amgen, BMS/Myokardia, Novo-Nordisk, Senior Associate Editor at ***Circulation***
- Executive steering committee member **REDUCE IT** trial

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

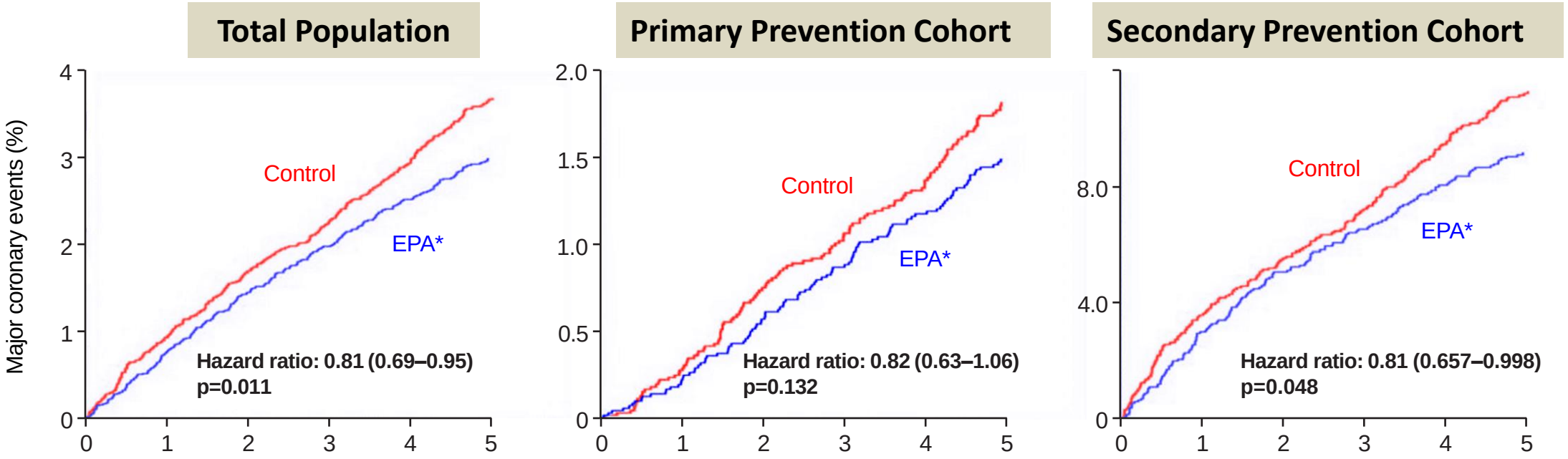
Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



Adapted with permission‡ from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [‡https://creativecommons.org/licenses.org/by-nc/4.0/]

JELIS shows CV Risk Reduction with 1.8 g/d EPA in Japanese Hypercholesterolemic Patients

18,645 patients with TC ≥ 6.5 mmol/l
Kaplan-Meier Estimates of Incidence of Coronary Events



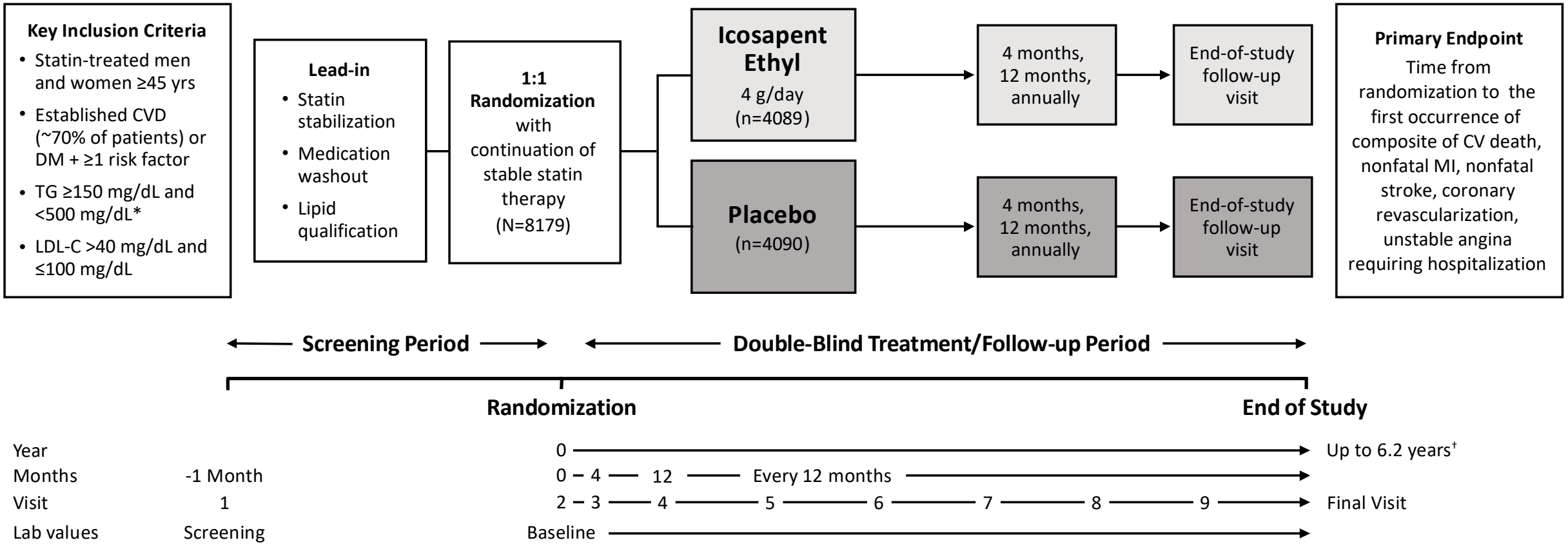
Numbers at risk						
Years	0	1	2	3	4	5
Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

Years	0	1	2	3	4	5
	7478	7204	7103	6841	6678	6508
	7503	7210	7020	6823	6649	6482

Years	0	1	2	3	4	5
	1841	1727	1658	1592	1514	1450
	1823	1719	1638	1566	1504	1442

Adapted with permission from Yokoyama et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. ***Lancet.*** 2007;369:1090-1098.

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.

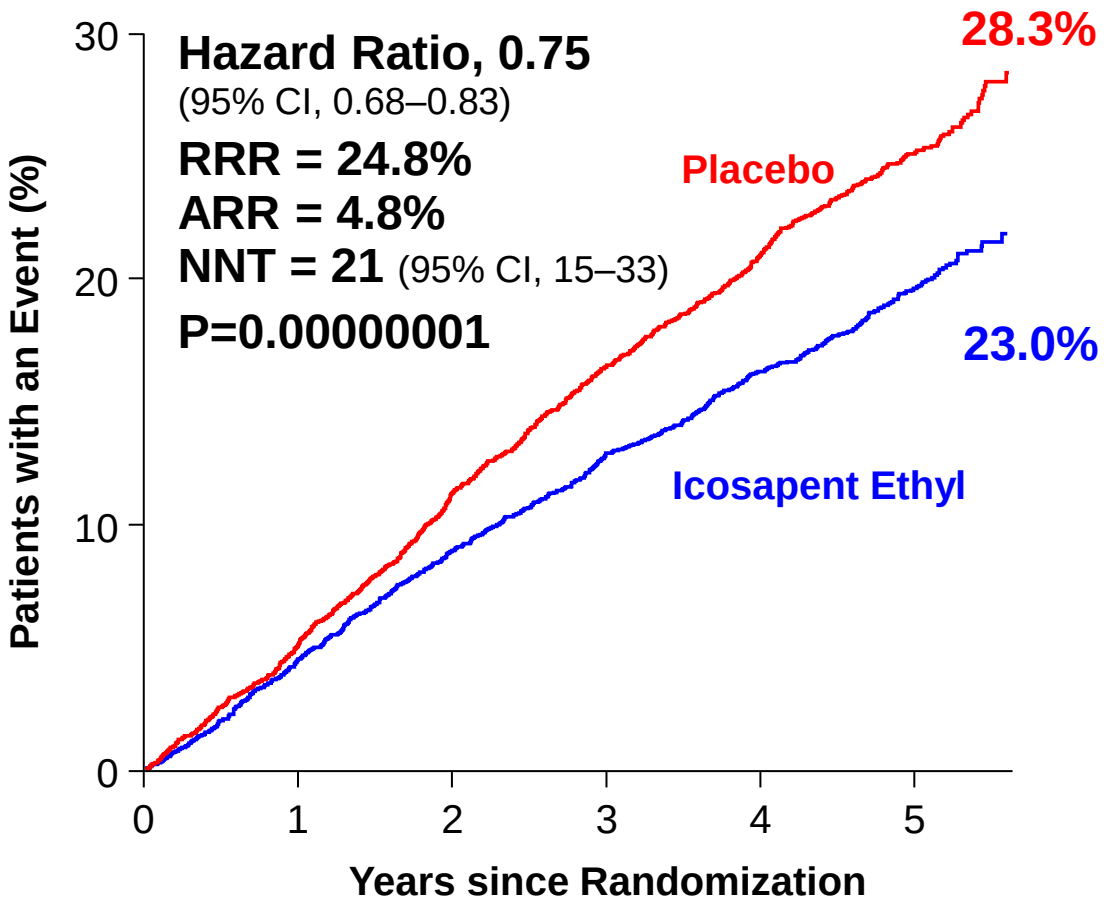
† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Adapted with permission‡ from Bhatt DL, Steg PG, Brinton EA, et al; on behalf of the REDUCE-IT Investigators. *Clin Cardiol*. 2017;40:138-148.
REDUCE-IT ClinicalTrials.gov number, NCT01492361. [‡https://creativecommons.org/licenses/by-nc/4.0/]

REDUCE IT: CV risk reduction with 4 g purified EPA/d in statin-treated pts at high risk with elevated TGs

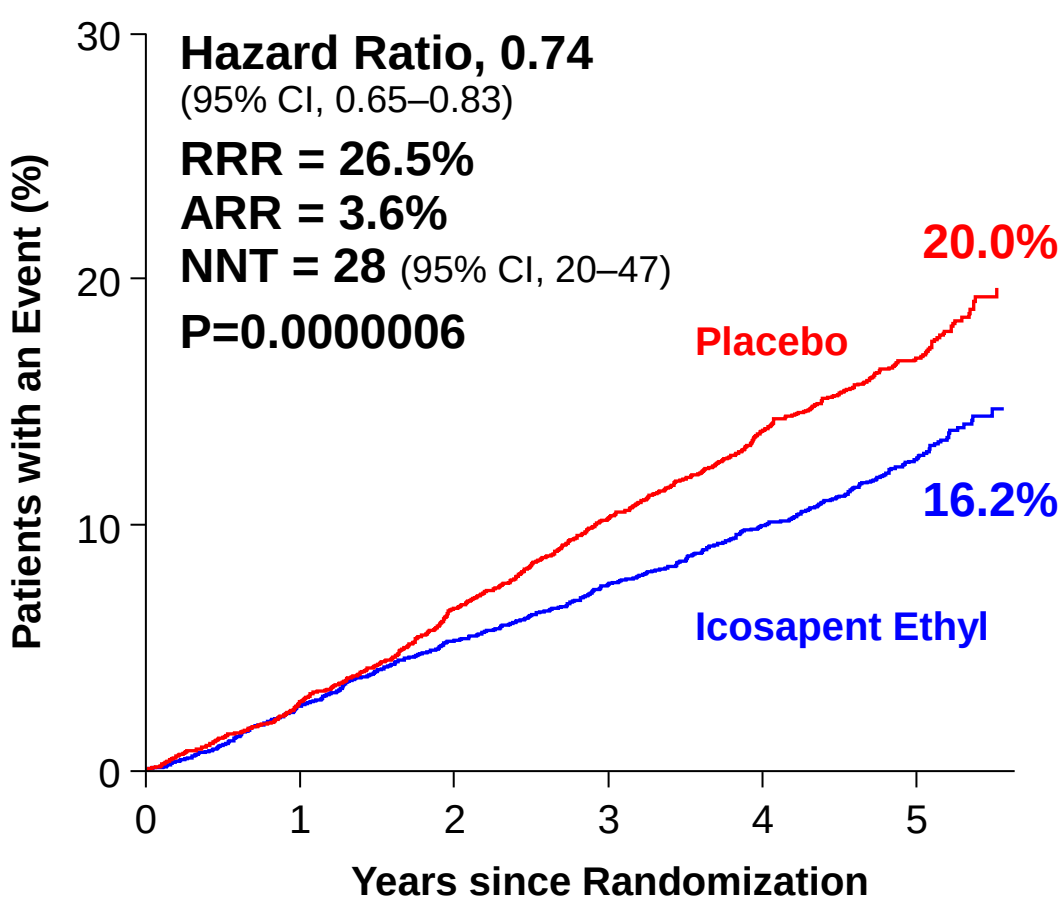
Primary Composite Endpoint:

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



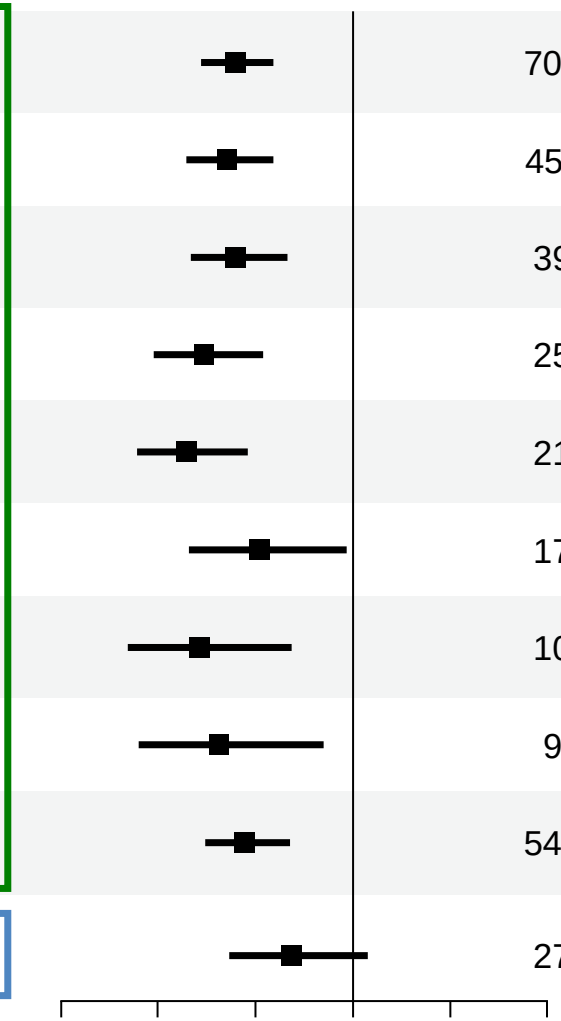
Key Secondary Composite Endpoint:

CV Death, MI, Stroke



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

Prespecified Hierarchical Testing

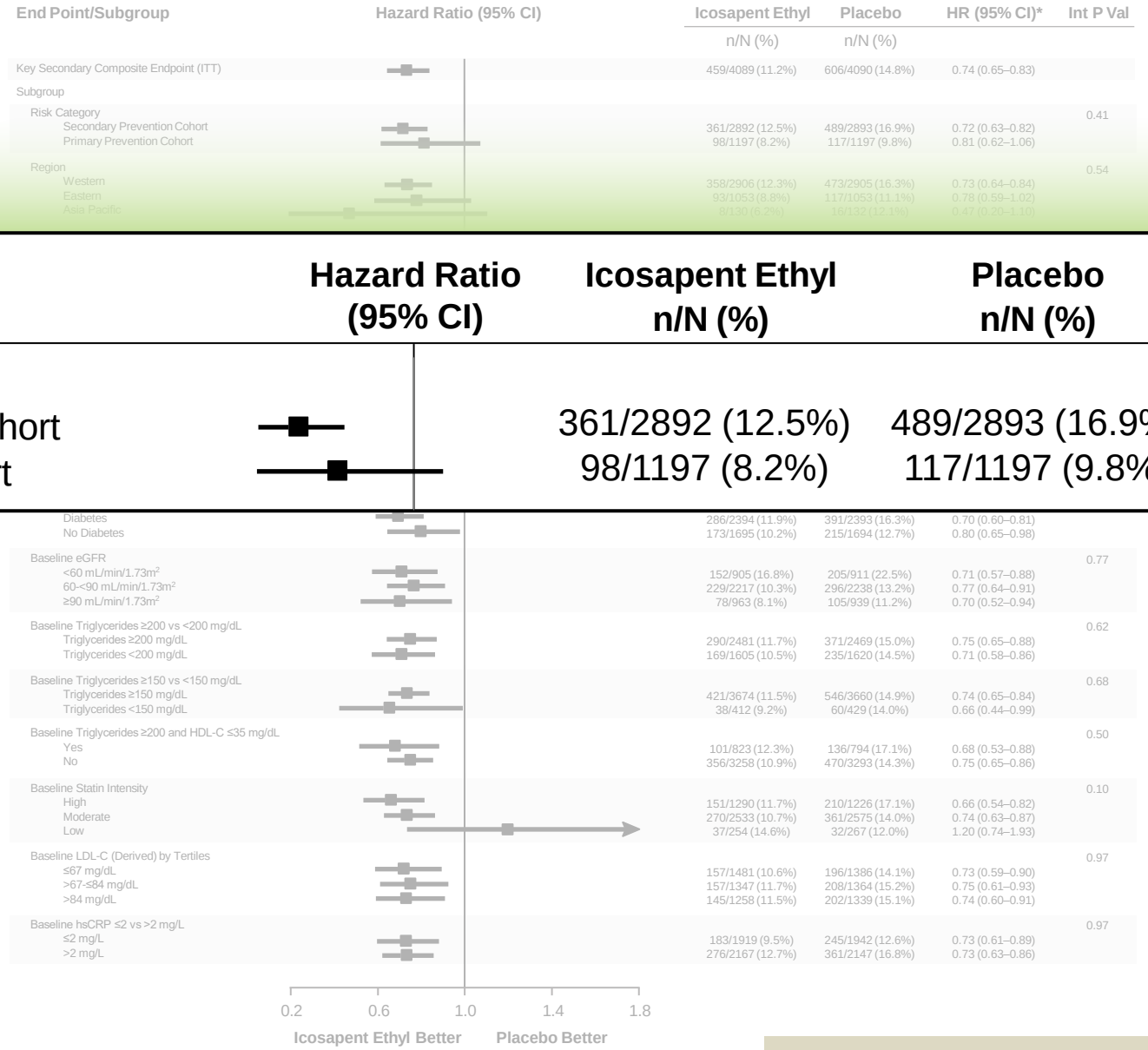


Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial 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

RRR denotes relative risk reduction

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

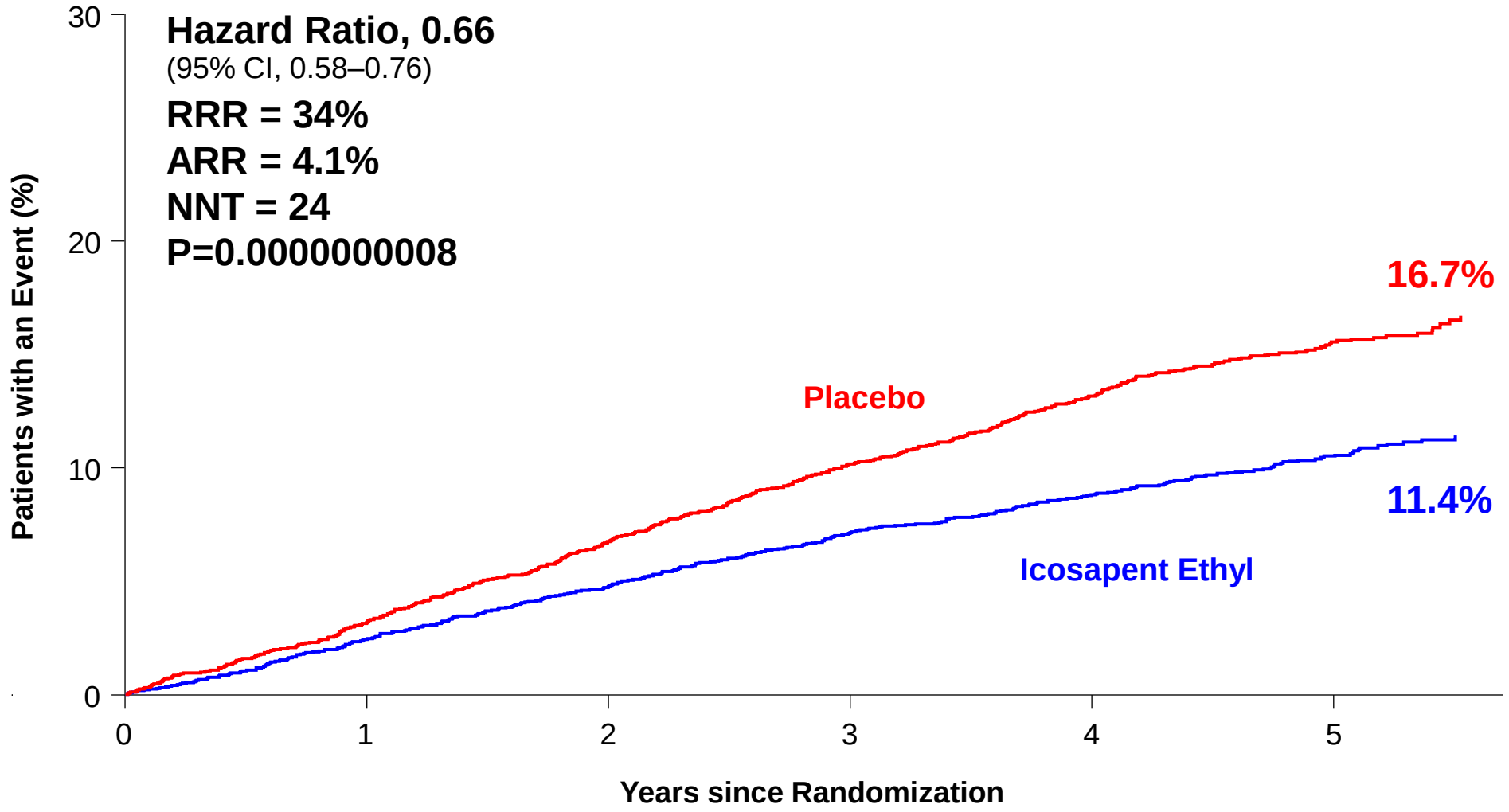
Key Secondary End Point in Subgroups



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Risk Category					0.41
Secondary Prevention Cohort		361/2892 (12.5%)	489/2893 (16.9%)	0.72 (0.63–0.82)	
Primary Prevention Cohort		98/1197 (8.2%)	117/1197 (9.8%)	0.81 (0.62–1.06)	

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

Time to Coronary Revascularization

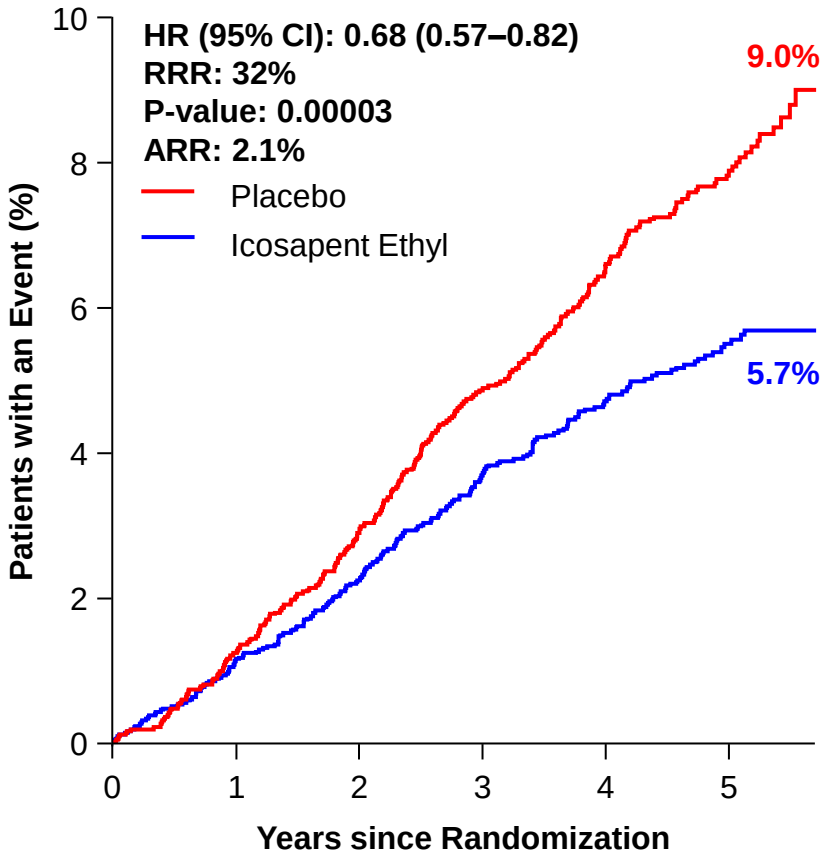


Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

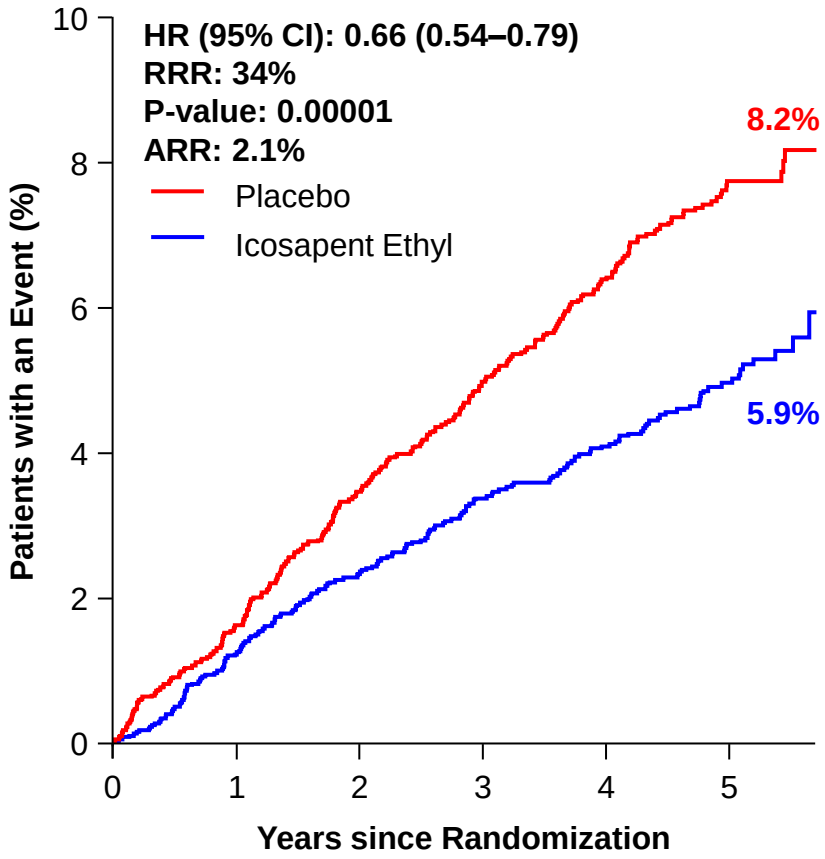
Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years. ARR is based on the observed rates of events of 9.2% for IPE and 13.3% for Placebo.

Time to Elective, Urgent, and Emergent Revascularization

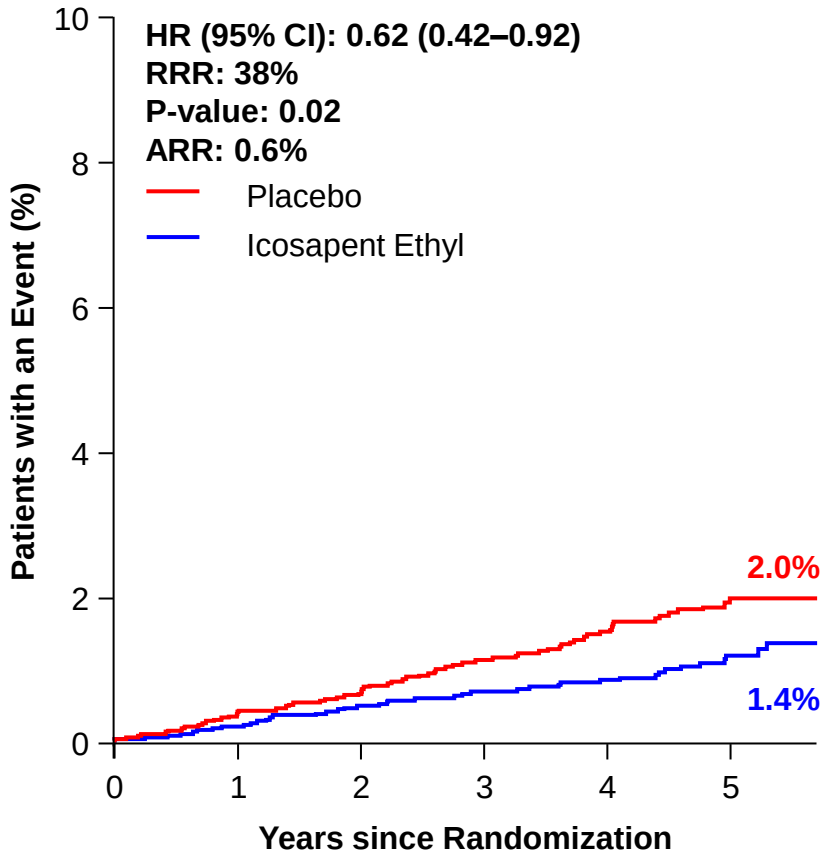
Time to Elective Coronary Revascularization



Time to Urgent Coronary Revascularization



Time to Emergent Coronary Revascularization

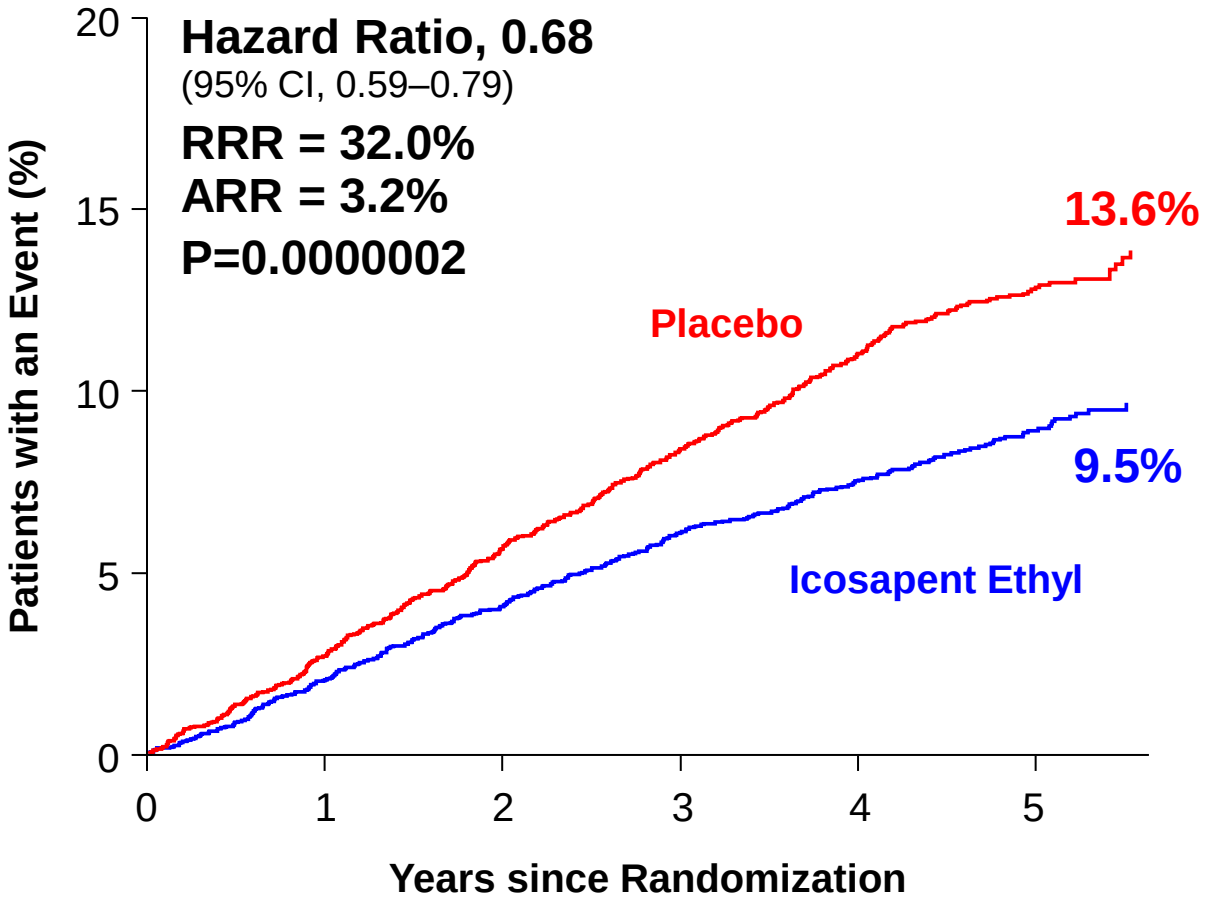


Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.
Time to Elective Revascularization ARR is based on the observed event rates of 4.7% for IPE and 6.8% for Placebo.
Time to Urgent Coronary Revascularization ARR is based on the observed rates of 4.4% for IPE and 6.6% for Placebo.
Time to Emergent Coronary Revascularization ARR is based on the observed event rates of 1.0% for IPE and 1.6% for Placebo.

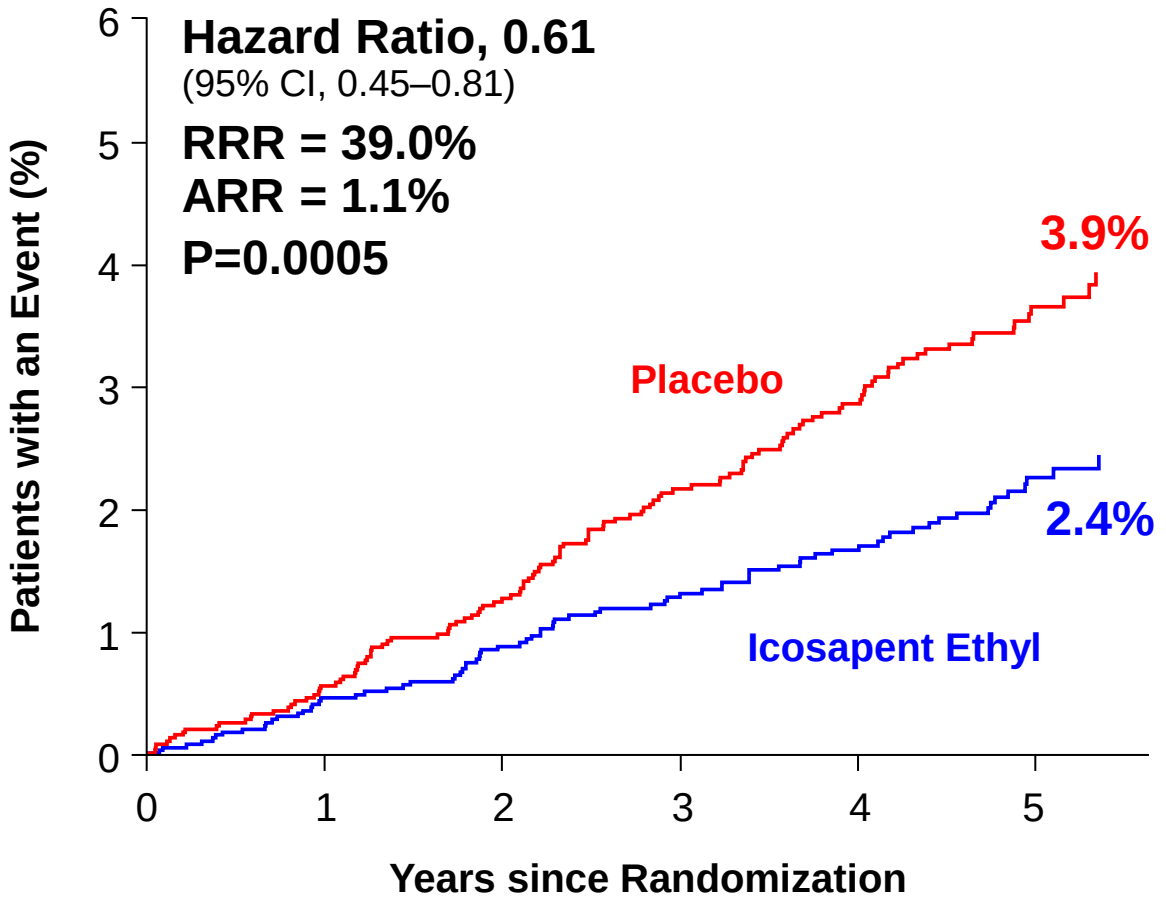
Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

Time to PCI and CABG

Time to Percutaneous Coronary Intervention



Time to Coronary Artery Bypass Graft



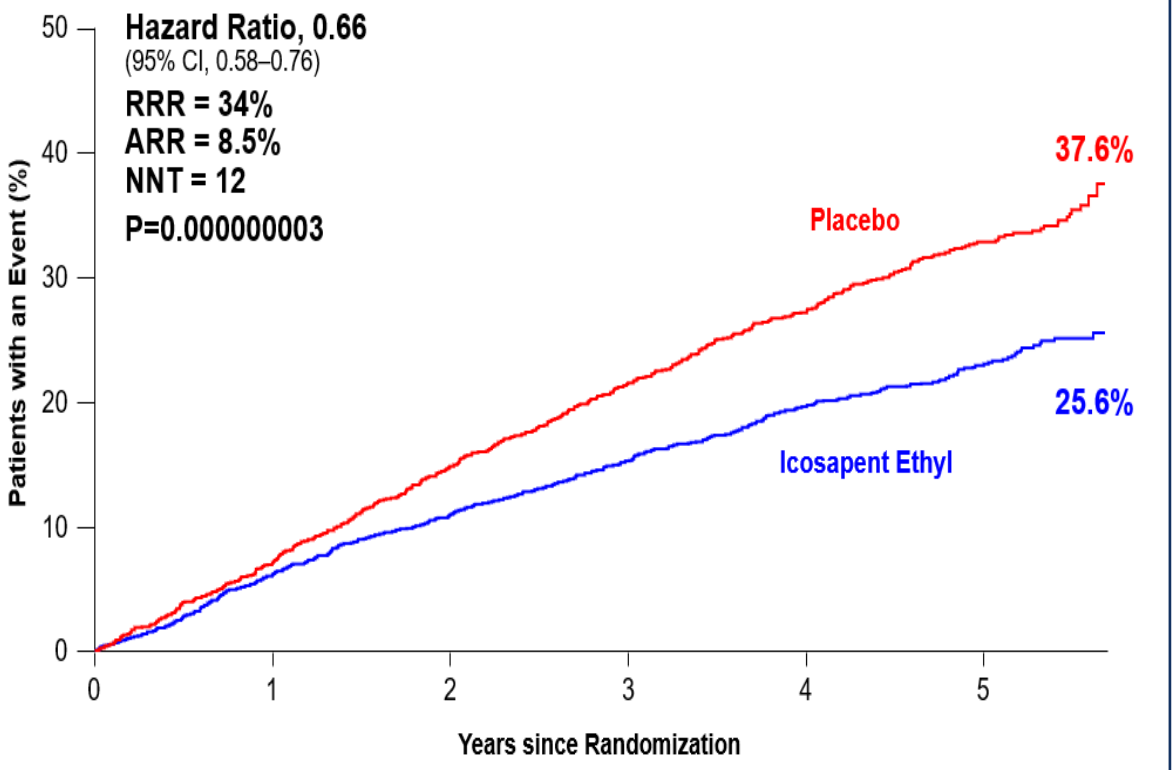
Estimated Kaplan-Meier event rate at approximately 5.7 years. The curves were visually truncated at 5.7 years.
Time to PCI ARR is based on the observed event rates of 7.7% for IPE and 10.9% for Placebo.
Time to CABG ARR is based on the observed event rates of 2.9% for IPE and 3.0% for Placebo.

Peterson BE, Bhatt DL, Steg PG, et al. *Circulation.* 2020.

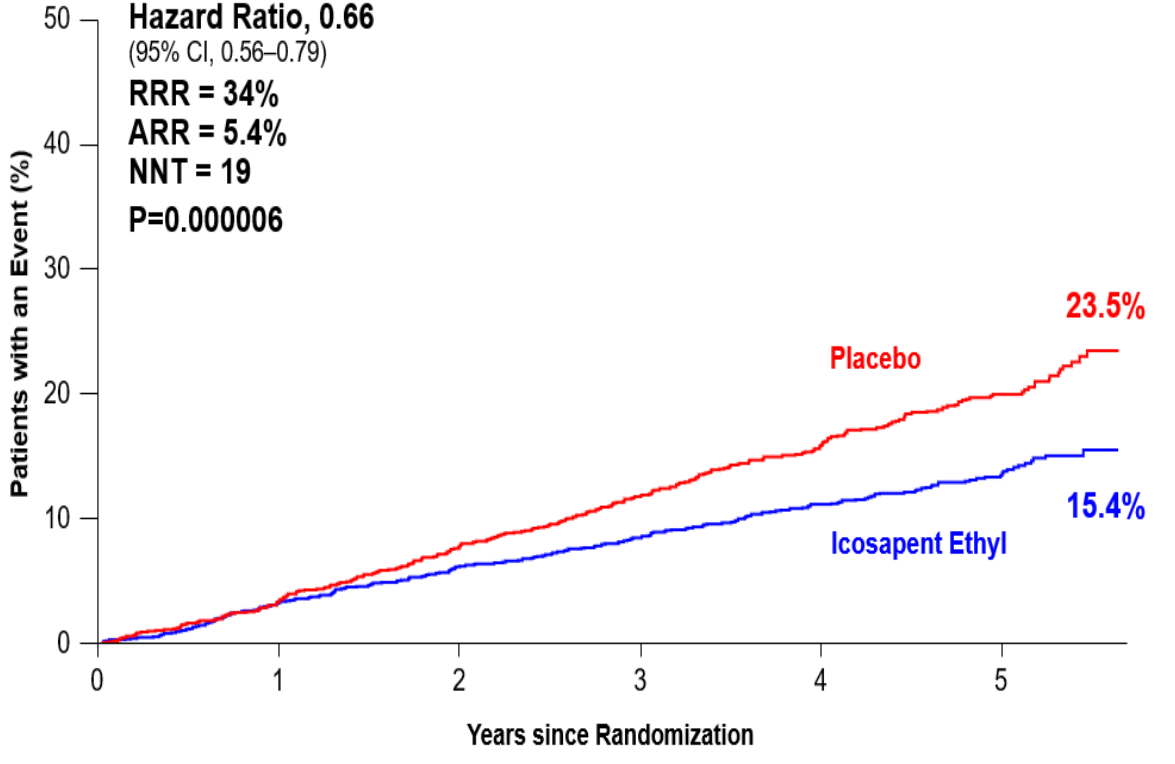
Benefit of Icosapent ethyl in Pts with a history of PCI

A post hoc analysis in 3408 pts

Primary Composite Endpoint



Key Secondary Composite Endpoint



Peterson BE et al. ***JAHA*** 2022;11.

Reduce-it: patients with prior MI, PCI or CABG

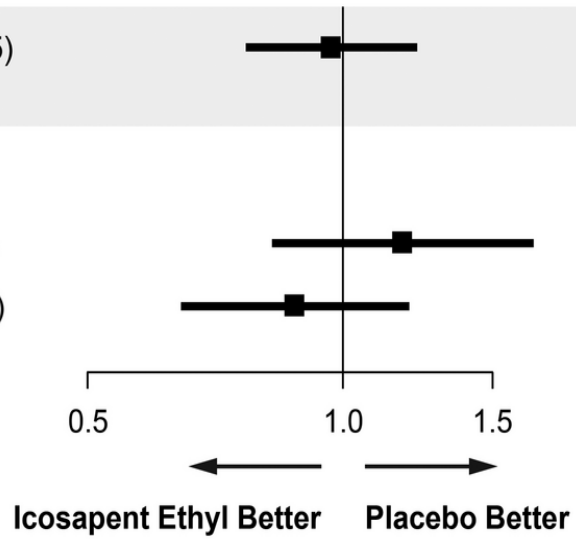
Primary endpoint					
	Icosapent-ethyl	**Placebo**	**HR**	**ARR**	**NNT$_{4.9yr}$**
All patients[1]	705/4098 (17.2)	901/4090 (22.0)	0.75 (0.68-0.83)	4.8	21
Prior MI[2]	378/1870 (20.2)	475/1823 (26.1)	0.74 (0.65-0.85)	5.9	17
Prior PCI[3]	362/1737 (20.8)	491/1671 (29.4)	0.66 (0.58-0.76)	8.5	12
Prior CABG[4]	179/897 (22.0)	265/940 (28.2)	0.76 (0.63-0.92)	6.2	16

1. Bhatt DL et al. ***N Engl J Med.*** 2019;380
2. Gaba P et al., ***JACC*** 2022;79;
3. Peterson BE et al. ***JAHA*** 2022; 11;
4. Verma S et al. ***Circulation*** 2021;144.

Icosapent ethyl did not reduce the risk for heart failure hospitalization compared with placebo, and this was not significantly different by history of prevalent heart failure.

Risk for heart failure requiring hospitalization by treatment assignment in patients with and without prevalent heart failure.

Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	Interaction P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*	
New Heart Failure Requiring Hospitalization (Adjudicated)	141/4089 (3.4)	144/4090 (3.5)	0.97 (0.77, 1.22)	
History of Heart Failure				0.25
Yes	65/703 (9.2)	59/743 (7.9)	1.17 (0.82, 1.67)	
No	76/3386 (2.2)	85/3344 (2.5)	0.88 (0.64, 1.19)	



Senthil Selvaraj. Journal of the American Heart Association. Impact of Icosapent Ethyl on Cardiovascular Risk Reduction in Patients With Heart Failure in REDUCE-IT, Volume: 11, Issue: 7, DOI: (10.1161/JAHA.121.024999)

What about safety ?

Treatment-Emergent Adverse Events

No Overall Treatment Difference in Adverse Event Profiles

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value*
Subjects with at Least One TEAE, n (%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug	88 (2.2%)	88 (2.2%)	>0.99
Serious TEAE Leading to Death	94 (2.3%)	102 (2.5%)	0.61

TEAE event rates represent the enrolled high CV risk patients and the 4.9-year median study follow-up.
* From Fisher's exact test.

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

Treatment-Emergent Adverse Event of Interest: Bleeding

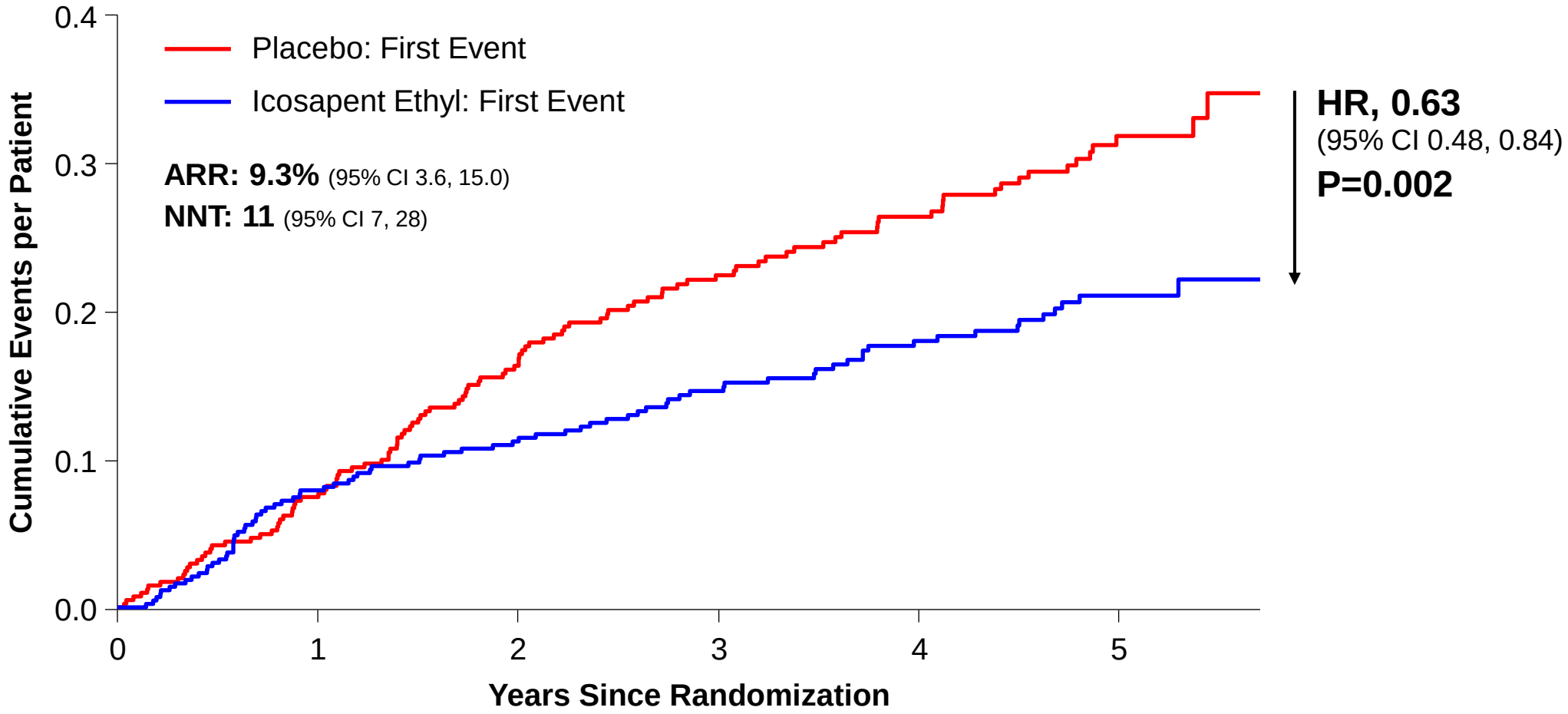
	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value*
All Bleeding TEAEs	482 (11.8%)	404 (9.9%)	0.006
Bleeding SAEs	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19
Intracranial Bleeding	0 (0.0%)	1(0.0%)	>0.99
Hemorrhagic Stroke	13 (0.3%)	10 (0.2%)	0.54

Note: Hemorrhagic stroke was an adjudicated endpoint; other bleeding events were included in safety analyses

* From Fisher's exact test.

Bhatt DL, Steg PG, Miller M, et al. ***N Engl J Med***. 2019; 380:11-22.
and ***FDA Advisory Committee***, 2019.

Time to First Event, Primary Composite Endpoint in Patients with Recent ACS <12 Months



No. at Risk:						
Placebo	407	395	373	311	253	150
Icosapent Ethyl	433	425	402	338	284	142

Steg PG, Bhatt DL, Miller M, et al. ACC 2023.

Treatment Emergent Bleeding Adverse Events or Hemorrhagic Stroke Endpoints in Patients with Recent ACS <12 Months

	Icosapent Ethyl (N=433)	Placebo (N=407)	Overall (N=840)	Fisher's Exact P-value
	n (%)	*n (%)*	*n (%)*	
Subjects with Any Bleeding TEAE or Hemorrhagic Stroke				
All Bleeding TEAEs	30 (6.9)	33 (8.1)	63 (7.5)	0.60
Bleeding SAEs	7 (1.6)	13 (3.2)	20 (2.4)	0.17
Gastrointestinal Bleeding	3 (0.7)	8 (2.0)	11 (1.3)	0.13
Central Nervous System Bleeding	1 (0.2)	1 (0.2)	2 (0.2)	1.00
Other Bleeding	3 (0.7)	4 (1.0)	7 (0.8)	0.72
Hemorrhagic Stroke	0 (0.0)	0 (0.0)	0 (0.0)	

Note: A treatment emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same grouped term are counted only once within each grouped term. Events that were positively adjudicated as clinical endpoints are not included.

Bleeding-related TEAEs are identified by the standardized MedDRA queries of 'Gastrointestinal haemorrhage', 'Central Nervous System haemorrhages and cerebrovascular conditions' and 'Haemorrhage terms (excl laboratory terms)'.

Note: Hemorrhagic stroke is an adjudicated endpoint.

Steg PG, Bhatt DL, Miller M, et al. ACC 2023.

Treatment Emergent Bleeding Adverse Events or Hemorrhagic Stroke Endpoints in Patients with Recent ACS <12 Months on Dual Anti-platelet Therapy at Baseline

	Icosapent Ethyl (N=287)	Placebo (N=297)	Overall (N=584)	Fisher's Exact P-value
	n (%)	*n (%)*	*n (%)*	
Subjects with Any Bleeding TEAE or Hemorrhagic Stroke				
All Bleeding TEAEs	22 (7.7)	28 (9.4)	50 (8.6)	0.46
Bleeding SAEs	5 (1.7)	11 (3.7)	16 (2.7)	0.20
Gastrointestinal Bleeding	2 (0.7)	7 (2.4)	9 (1.5)	0.18
Central Nervous System Bleeding	0 (0.0)	1 (0.3)	1 (0.2)	1.00
Other Bleeding	3 (1.0)	3 (1.0)	6 (1.0)	1.00
Hemorrhagic Stroke	0 (0.0)	0 (0.0)	0 (0.0)	

Note: Dual anti-platelet therapy is two or more anti-platelet therapies.

Note: A treatment emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same grouped term are counted only once within each grouped term. Events that were positively adjudicated as clinical endpoints are not included.

Bleeding-related TEAEs are identified by the standardized MedDRA queries of 'Gastrointestinal haemorrhage', 'Central Nervous System haemorrhages and cerebrovascular conditions' and 'Haemorrhage terms (excl laboratory terms)'.

Note: Hemorrhagic stroke is an adjudicated endpoint.

Steg PG, Bhatt DL, Miller M, et al. ACC 2023.

Atrial Fibrillation or Flutter

- Atrial fibrillation/flutter requiring hospitalization ≥24 hours was an adjudicated efficacy endpoint
- All other atrial fibrillation/flutter events reside in the safety database

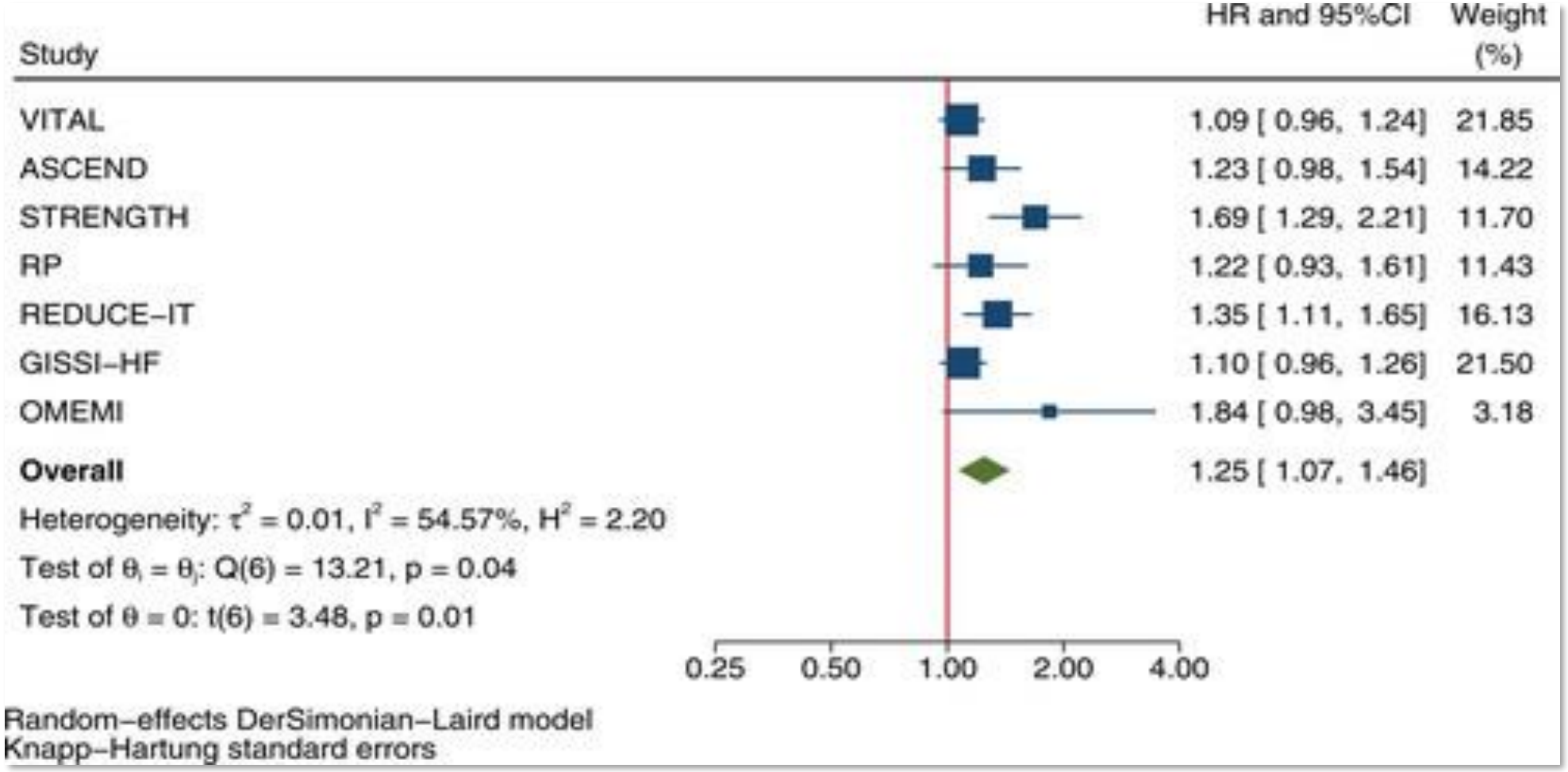
	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value*
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[1]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[2]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization[3]	127 (3.1)	84 (2.1)	0.004

Note: Clinical consequences, including stroke, MI, cardiac arrest, and sudden cardiac death were reduced in the overall ITT population, with consistent results in those with a history of atrial fibrillation at baseline.

* From Fisher's exact test.

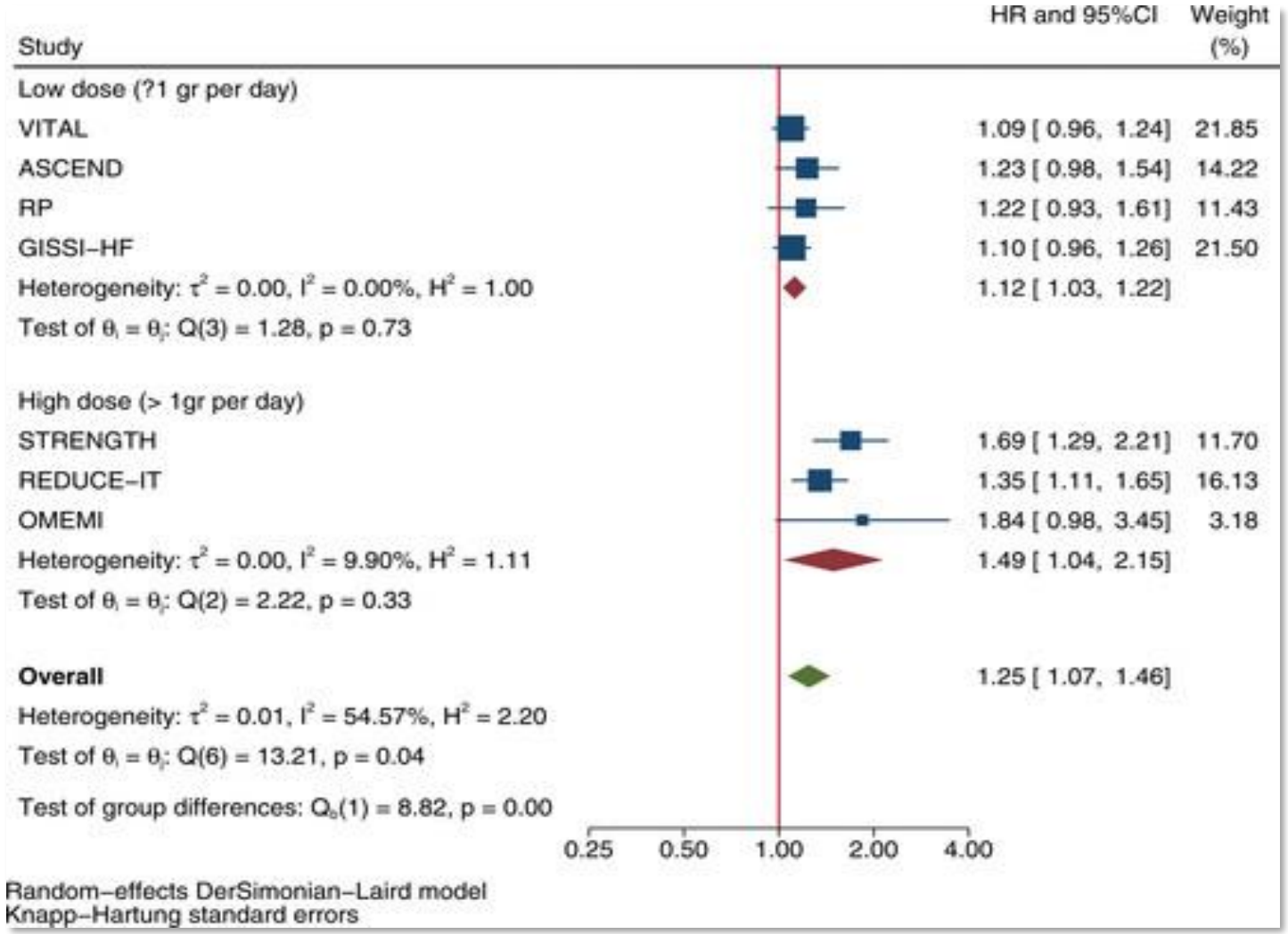
1. Includes atrial fibrillation/flutter TEAEs. 2. Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. 3. Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization clinical events by the Clinical Endpoint Committee.

Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in RCTs of CV Outcomes: A Systematic Review and Meta-Analysis



Gencer et al. ***Circulation***., 2022;144 : 1981-1990

Effect of marine ω-3 fatty acids supplements on the risk of atrial fibrillation events stratified by low dose (≤1 g/d) versus high dose (>1 g/d)



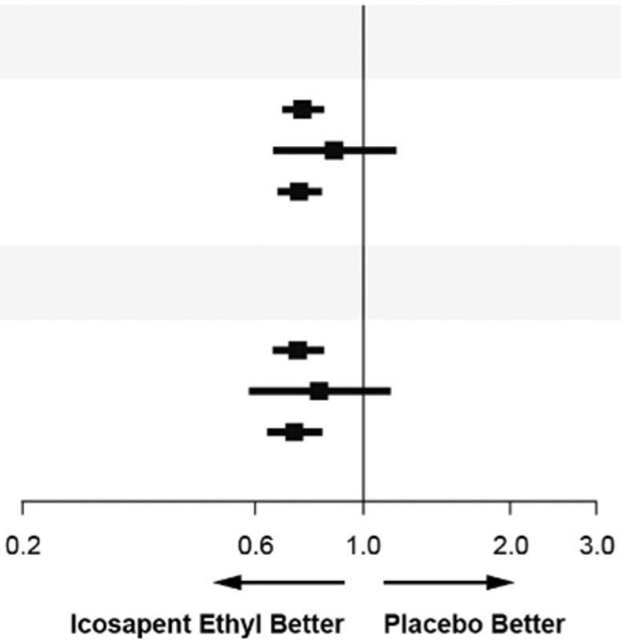
Knapp-Hartung adjustment for random effect model

Gencer et al. ***Circulation***., 2022;144 : 1981-1990

Benefits of IPE were consistent regardless of AFib/flutter at baseline

Endpoints with or without atrial fibrillation/flutter at baseline

	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value	Interaction P-value
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Primary Composite Endpoint					
All patients (ITT)	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	<0.0001	
With prior AF	87/368 (23.6)	98/383 (25.6)	0.87 (0.65, 1.17)	0.36	0.37
Without prior AF	618/3721 (16.6)	803/3707 (21.7)	0.74 (0.67, 0.82)	<0.0001	
Key Secondary Composite Endpoint					
All patients (ITT)	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	<0.0001	
With prior AF	64/368 (17.4)	75/383 (19.6)	0.81 (0.58, 1.14)	0.23	0.55
Without prior AF	395/3721 (10.6)	531/3707 (14.3)	0.72 (0.64, 0.82)	<0.0001	



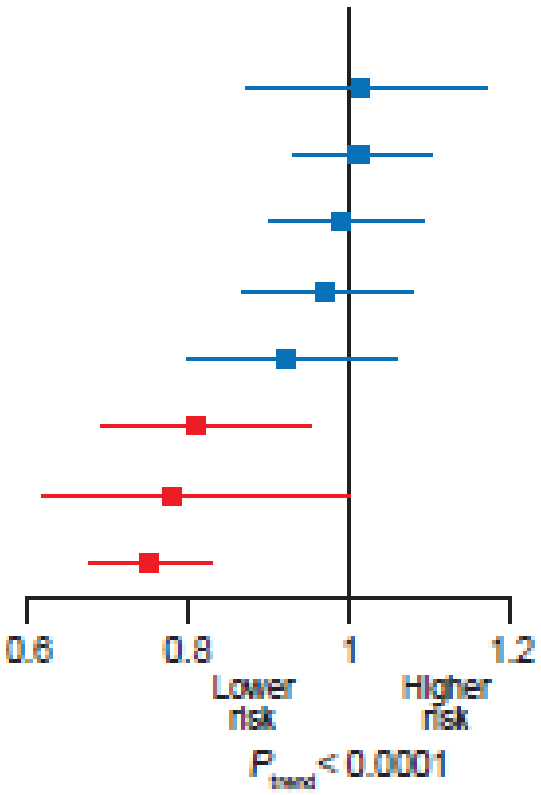
Olshansky B et al ***JAHA*** 2023

Benefits of Omega-3 Fatty Acids in ASCVD Risk Reduction

- Robust benefit of IPE in JELIS and REDUCE-IT
- **Contrasting results of EPA DHA vs EPA**

Major randomized CV outcomes trials of O3FA

Trial	n	Treatment	Outcome	HR (95% CI)
ALPHA OMEGA	4837	226 mg EPA, 150 mg DHA	CV events, PCI, CABG	1.01 (0.87–1.17)
ORIGIN	12,536	0.9 g EPA DHA	MACE	1.01 (0.93–1.10)
STRENGTH	13,086	4 g EPA-DHA	CVD, MI, stroke, revasc, UA, H	0.99 (0.90–1.09)
ASCEND	15,480	1 g EPA DHA	MI, stroke/TIA, CVD	0.97 (0.87–1.08)
VITAL	25,871	1 g EPA DHA	CVD, MI stroke	0.92 (0.80–1.06)
JELIS	18,645	1.8 g EPA	Coronary events	0.81 (0.69–0.95)
RESPECT EPA	2506	1.8 g EPA	CVD, MI, stroke, revasc, UA, H	0.78 (0.62–1.00)
REDUCE IT	8179	4 g EPA	CVD, MI, stroke, revasc, UA, H	0.75 (0.68–0.83)



Benefits of Omega-3 Fatty Acids in ASCVD Risk Reduction

- Robust benefit of IPE in JELIS and REDUCE-IT
- Correlated to achieved EPA levels
- Contrasting results of EPA DHA vs EPA
- **Effects of mineral oil**

Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
Biomarker*	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

*Apo B and hsCRP were measured at Year 2.

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

FDA statements on hypothetical effects of mineral oil in REDUCE IT

- an exploratory analysis indicates that the effect of LDL-C values on the time to the primary endpoint is numerically small and unlikely to change the overall conclusion of treatment benefit.

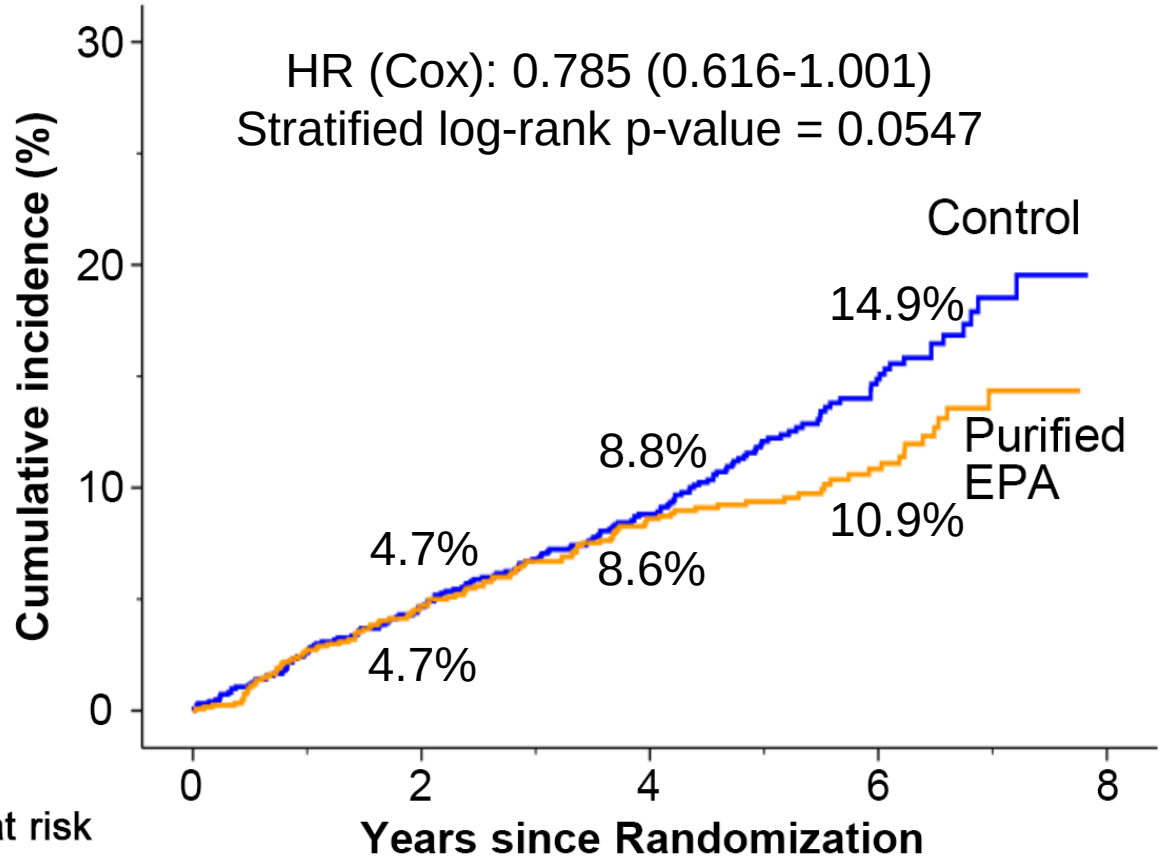
- Largest LDL-C differential per FDA analyses would translate to *a maximal possible impact of approximately 3.1% points of the observed 25% RRR*

- Prior trial reported a CV benefit with EPA consistent with REDUCE-IT
  - 19% RRR reported in JELIS, which did not include a placebo

FDA Briefing document https://www.fda.gov/media/132477/download

RESPECT EPA: Primary and Secondary Endpoints

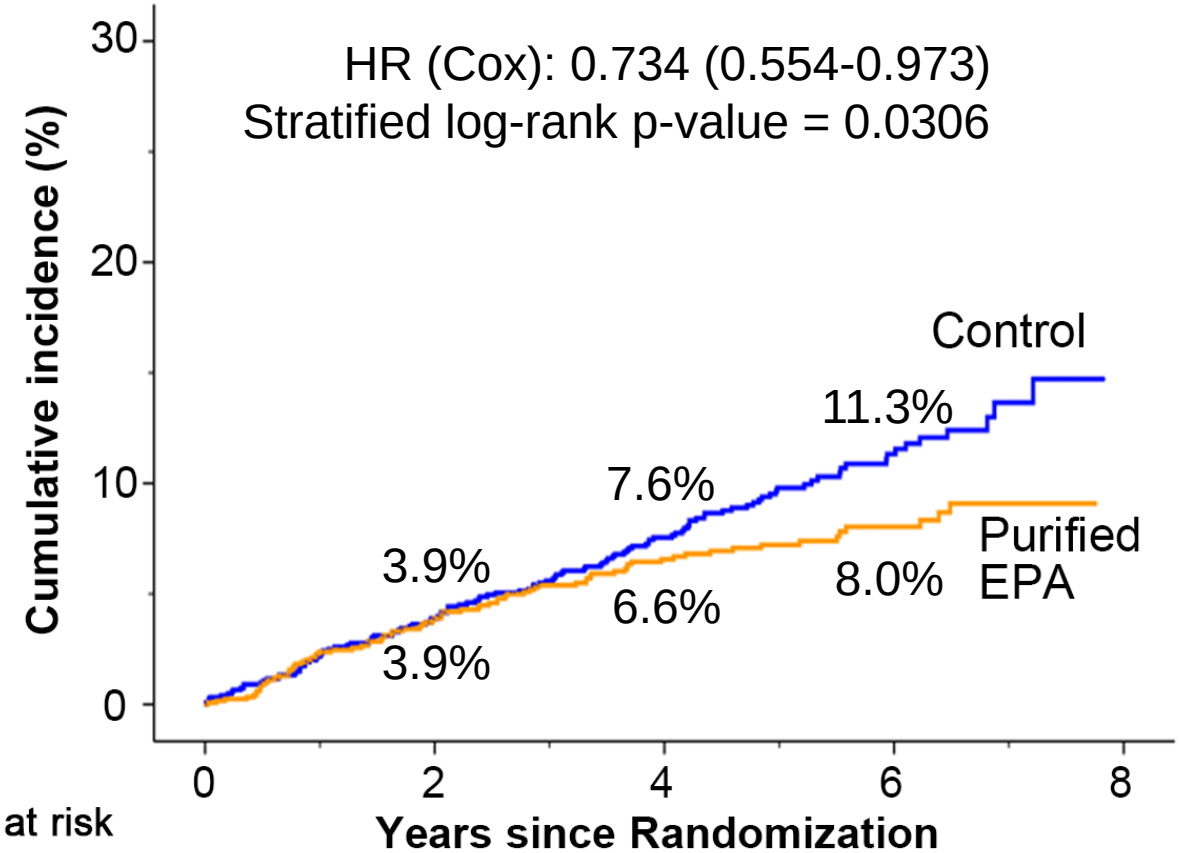
Primary Endpoint*



No. at risk				
Control	1235	1087	909	382
Purified EPA	1225	982	793	352

*: The composite of CV death, nonfatal MI, nonfatal Ischemic stroke, unstable angina, coronary revascularization)

Secondary Endpoint**



No. at risk				
Control	1235	1093	913	387
Purified EPA	1225	988	801	355

**: Sudden cardiac death, MI, unstable angina, coronary revascularization

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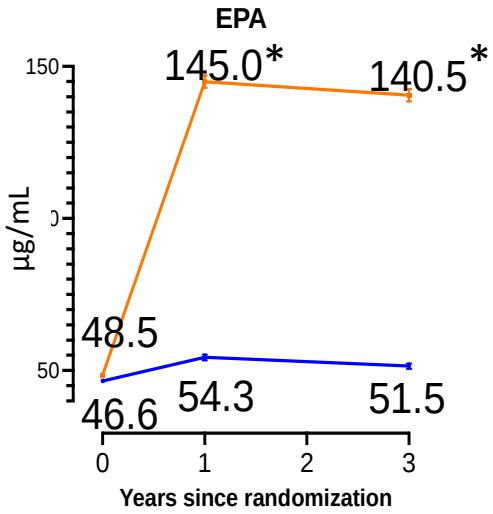
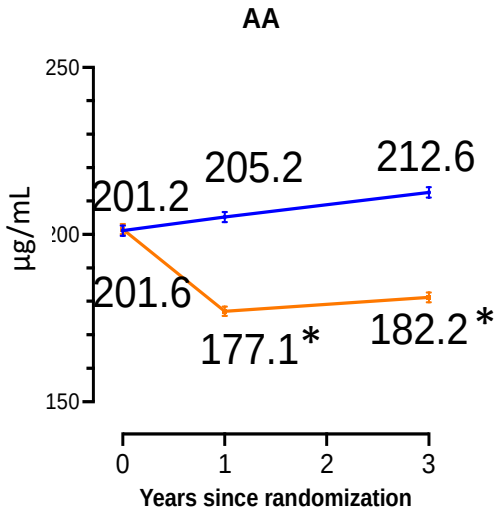
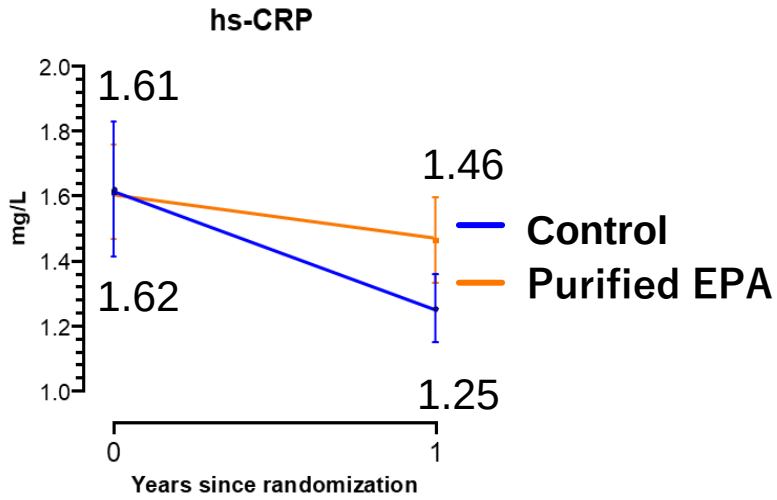
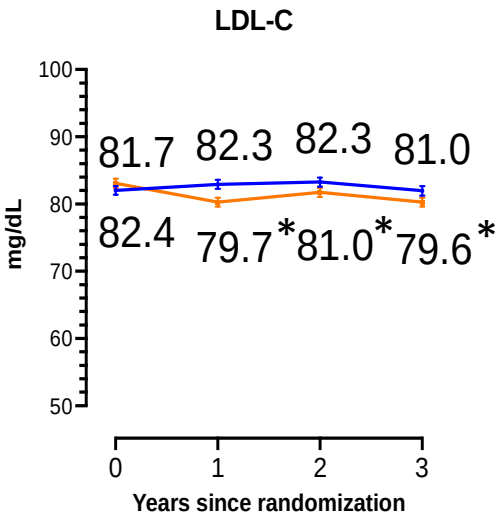
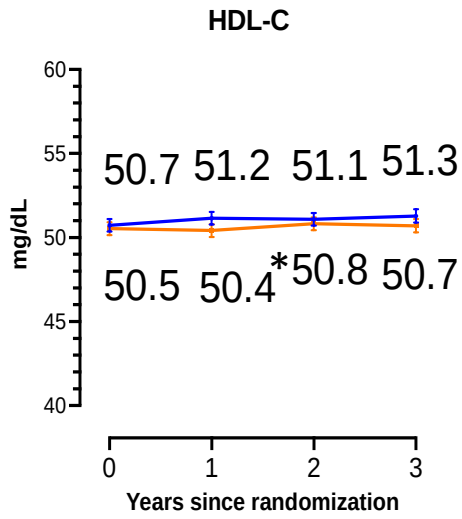
RESPECT EPA: Changes in Fatty Acids, Lipid and hs-CRP

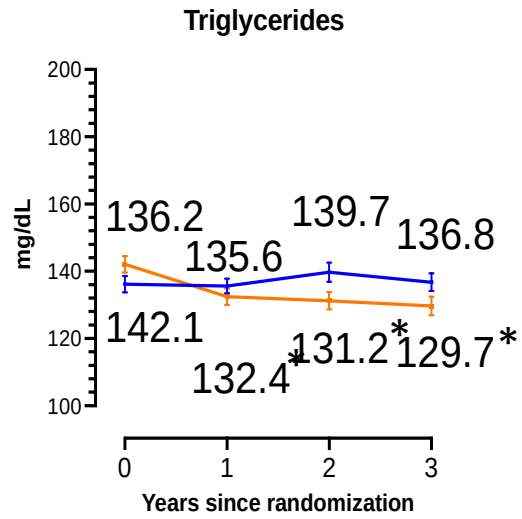












*: p<0.05 compared to baseline level by analysis of covariance

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Benefits of Omega-3 Fatty Acids in ASCVD Risk Reduction

- Robust benefit of IPE in JELIS and REDUCE-IT
- Contrasting results of EPA DHA vs EPA
- Effects of mineral oil
- **What are the mechanisms for benefit ?**

The benefit of IPE is independent of baseline TGs

Key Secondary End Point in Subgroups

Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.68
Triglycerides ≥150 mg/dL		421/3674 (11.5%)	546/3660 (14.9%)	0.74 (0.65–0.84)	
Triglycerides <150 mg/dL		38/412 (9.2%)	60/429 (14.0%)	0.66 (0.44–0.99)	

Icosapent Ethyl Better Placebo Better

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

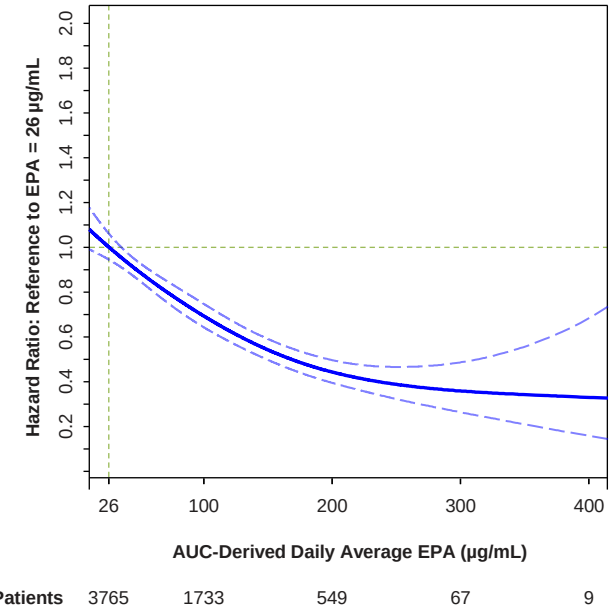
The benefit is highly correlated to on-treatment EPA levels

Dose-Response of Hazard Ratio (95% CI)

Primary Composite Endpoint by On-Treatment Serum EPA

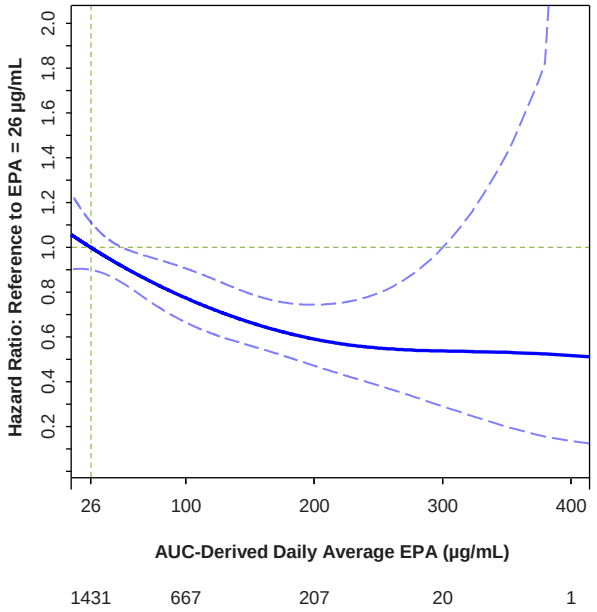
Established Cardiovascular Disease or Diabetes with Risk Factors

Primary Endpoint: Established Cardiovascular Disease[1-5]



No. of Patients	3765	1733	549	67	9

Primary Endpoint: Diabetes with Risk Factors[1-5]



No. of Patients	1431	667	207	20	1

Dose-response hazard ratio ——— 95% Confidence Interval (CI) - - - -

P*<0.001 for all

Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance[1], age[2], sex[3], baseline diabetes[4], hsCRP[5].
***P value is <0.001 for both non-linear trend and for regression slope.**

Bhatt DL. ACC/WCC 2020, Chicago (virtual).

Conclusions

- Clinical trials using low doses of O3FA for CV prevention have yielded inconsistent results
- Modern clinical trials using EPA-DHA have not shown CV benefit
- Three trials using high doses of EPA have shown robust CV benefit
  - JELIS and RESPECT-EPA in comparison to usual care (no placebo control)
  - REDUCE IT in comparison to mineral oil
  - Safety profile appears good, but atrial Fib/flutter is increased and bleeding risk may be increased
- The mechanisms of benefit remain speculative but may include antithrombotic and anti-inflammatory effects. Benefit appears strongly correlated to achieved EPA levels, but not to TGs, LDL-C, or hs-CRP