Perspectives on the results of recent clinical outcomes trials with EPA

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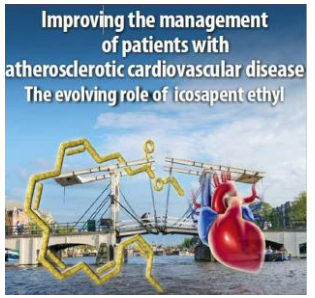
Improving the management of patients with atherosclerotic cardiovascular disease - The evolving role of icosapent ethyl



PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

Disclosures

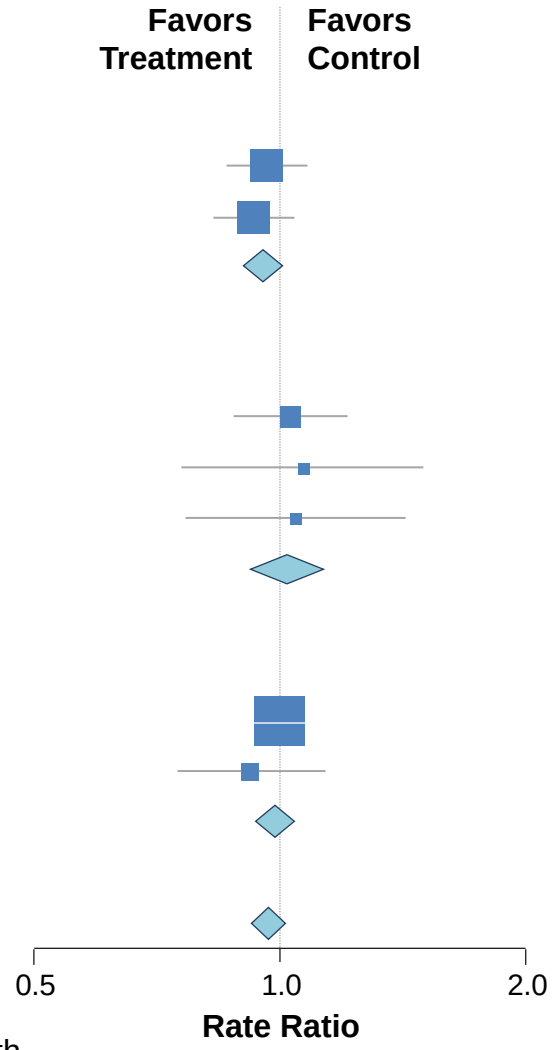
- **Research grants** : Amarin, Bayer, Sanofi, and Servier
- **Clinical Trials (Steering committee, CEC, DSMB)** : Amarin, AstraZeneca, Bayer, Bristol-Myers Squibb, Idorsia, Janssen, Novartis, Pfizer, Sanofi, Servier
- **Consulting or speaking**: Amarin, Amgen, BMS/Myokardia, Novo-Nordisk,
- Senior Associate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

Clinical outcomes data with EPA

- Background to REDUCE IT: JELIS

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

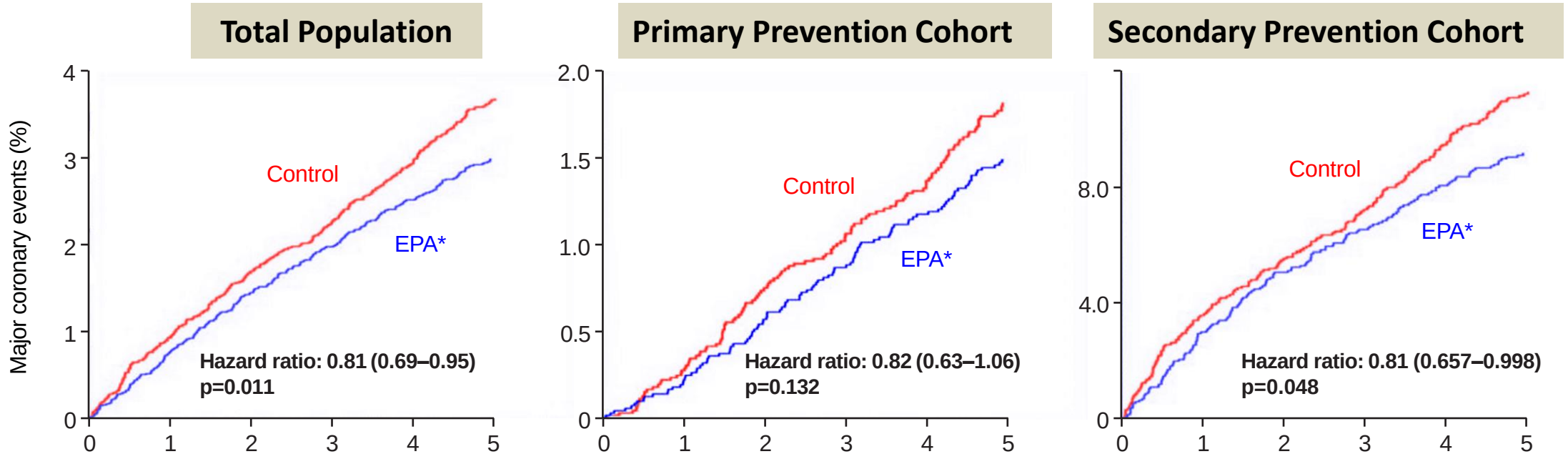
Source	No. of Events (%)		Rate Ratios (CI)
	Treatment	Control	
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	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.

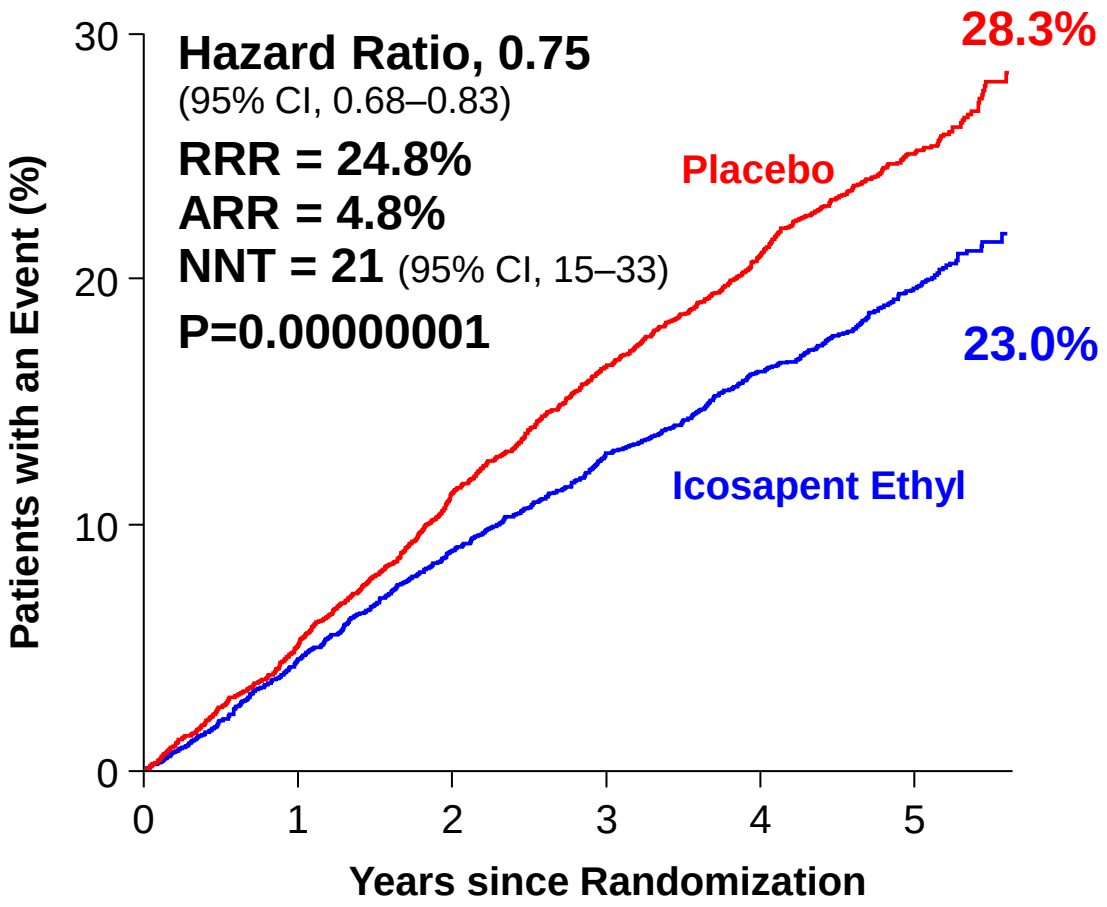
Clinical outcomes data with EPA

- Background to REDUCE IT: JELIS
- **REDUCE IT main results**

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

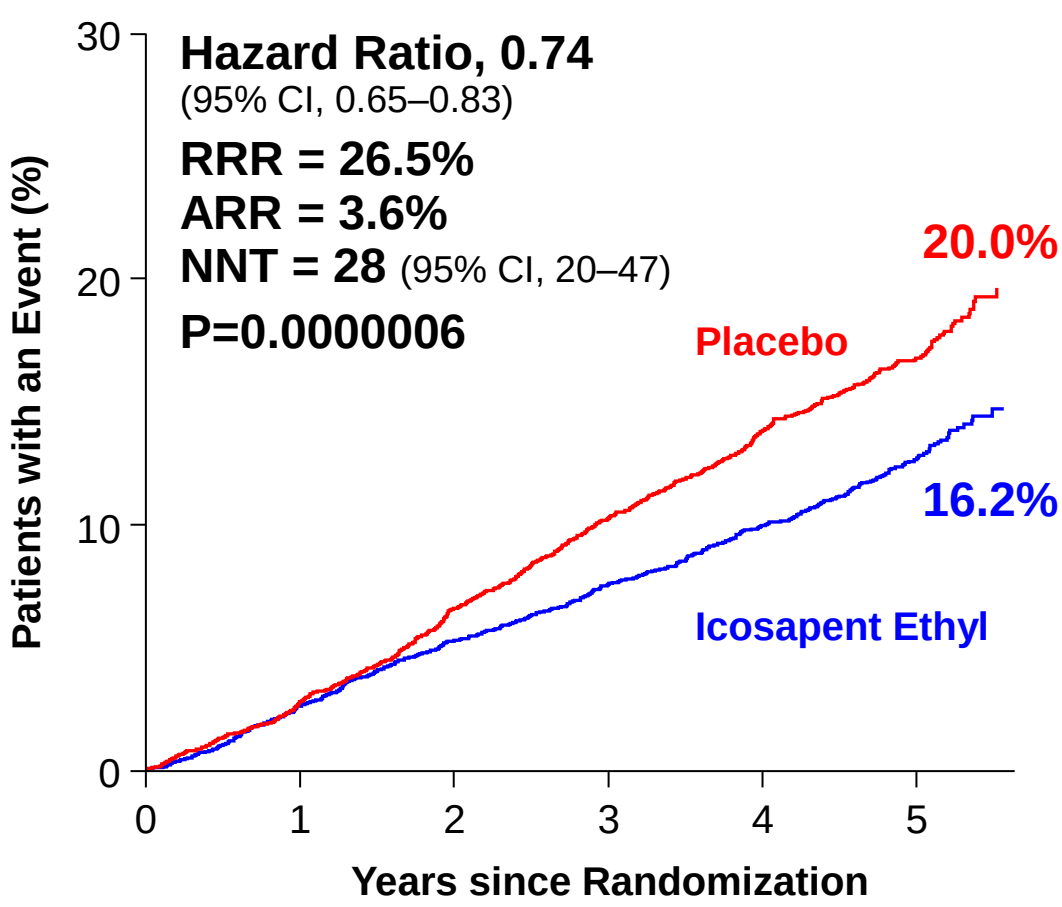
Primary Composite Endpoint:

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



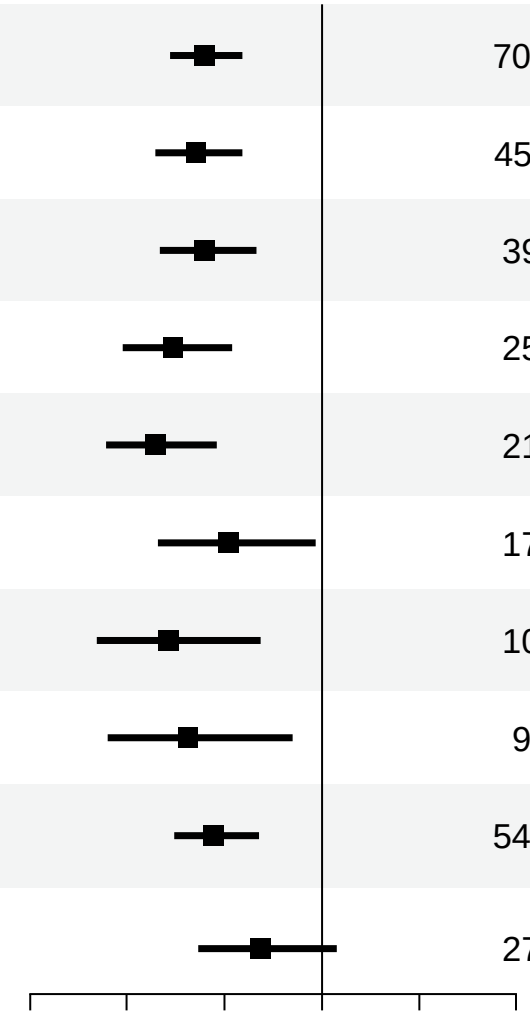
Key Secondary Composite Endpoint:

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.

Clinical outcomes data with EPA

- Background to REDUCE IT: JELIS
- REDUCE IT main results
- **Safety of Icosapent Ethyl**

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.

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

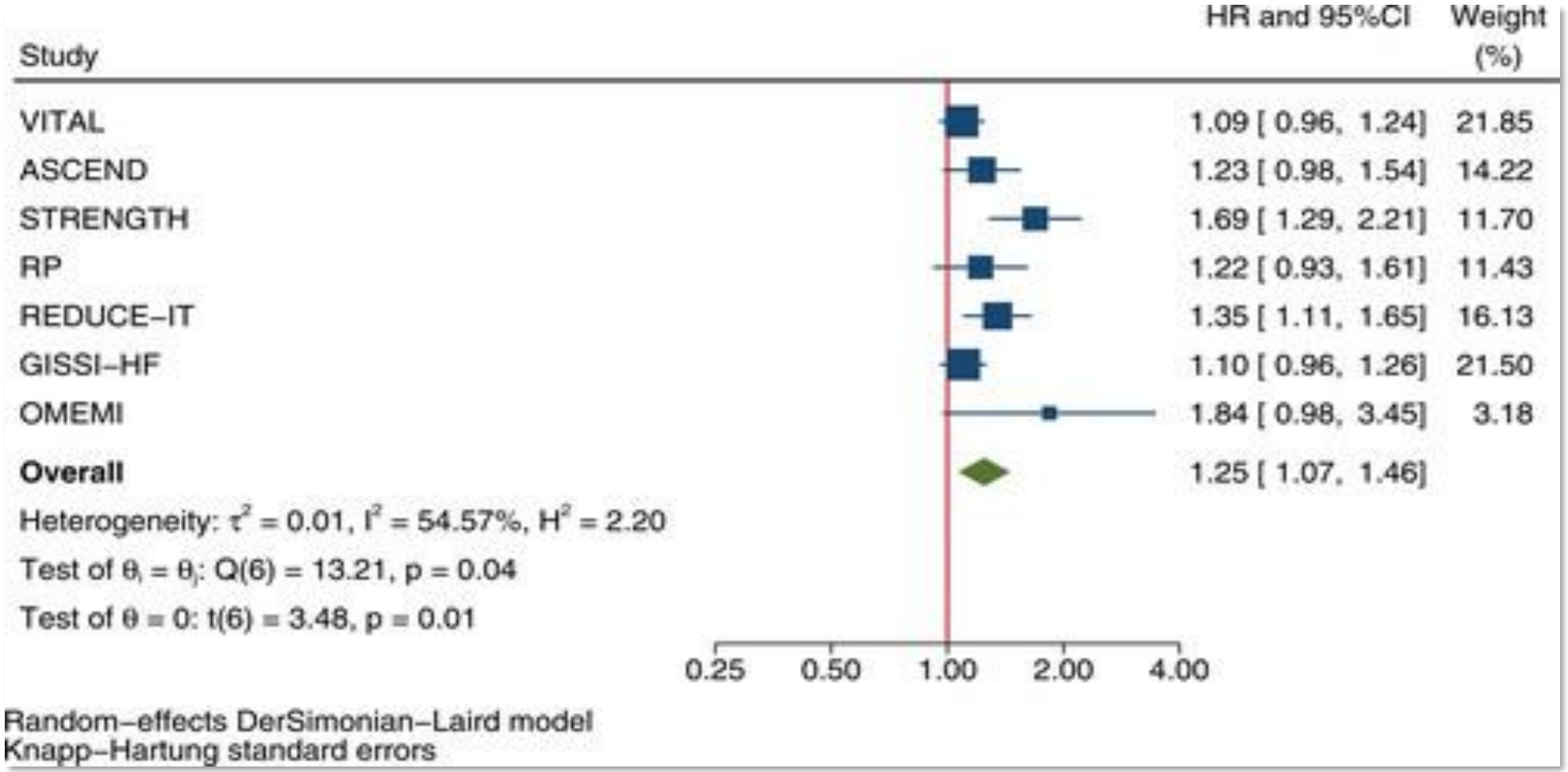
	Icosapent Ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-value*
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[1]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[2]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated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

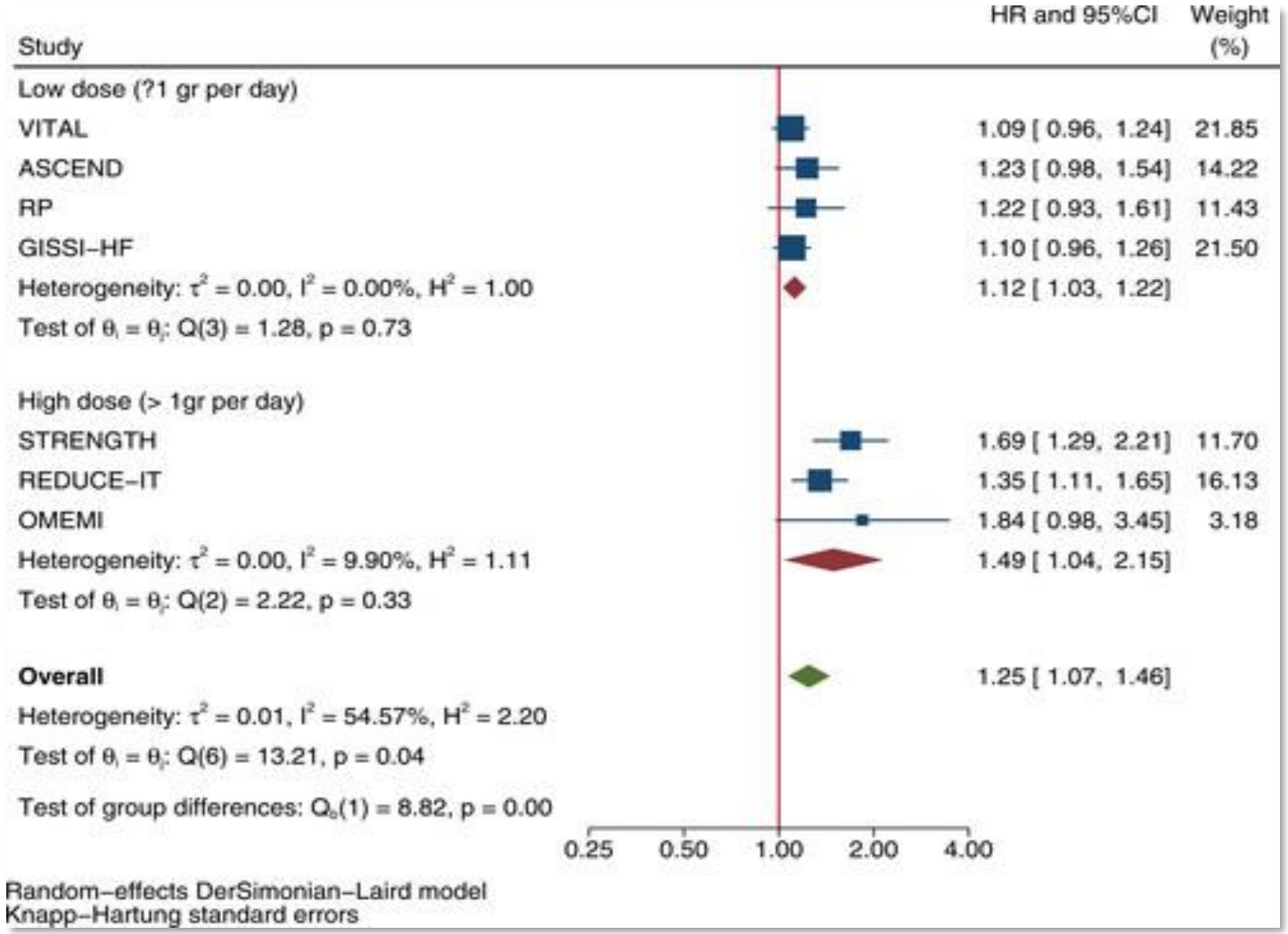
1. Includes atrial fibrillation/flutter TEAEs. 2. Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. 3. Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization clinical events by the Clinical Endpoint Committee.

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)



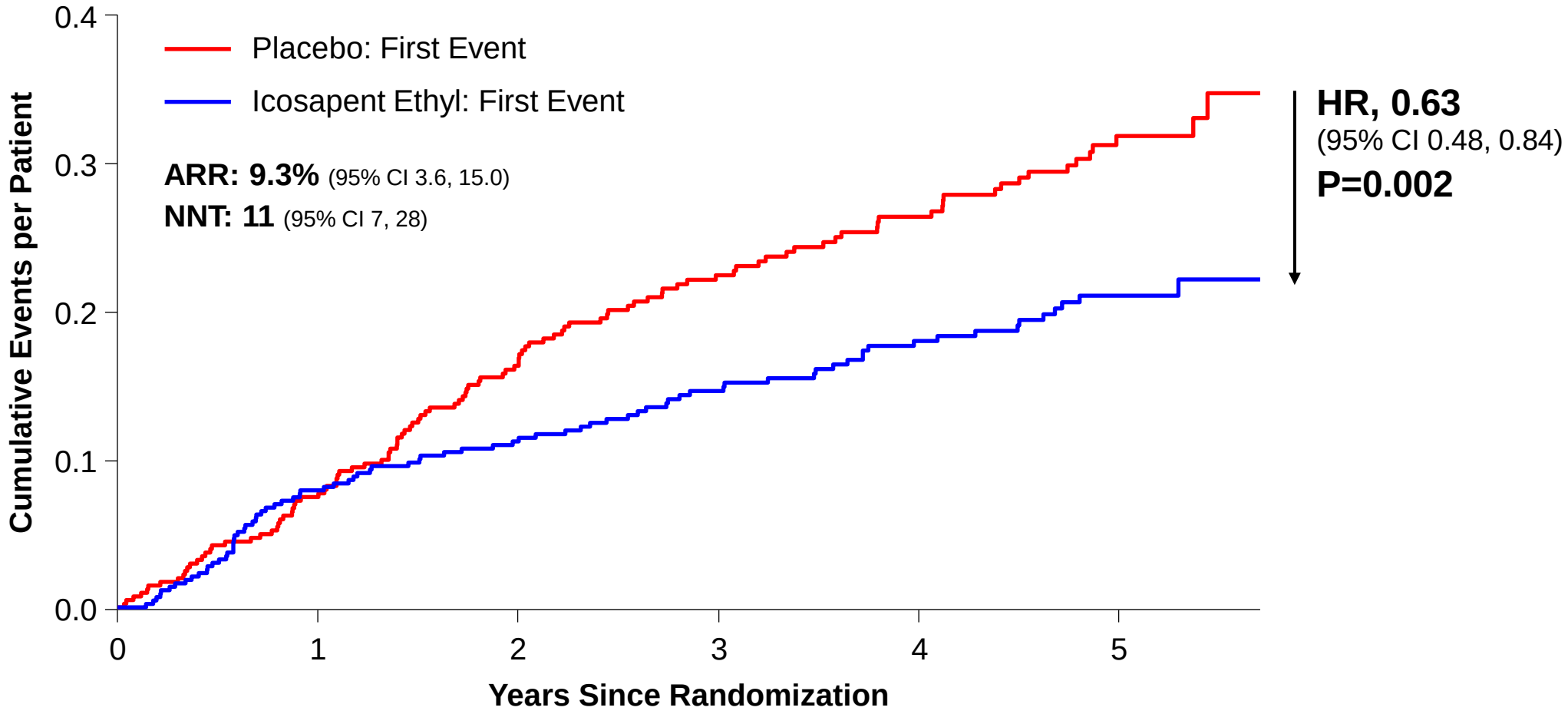
Knapp-Hartung adjustment for random effect model

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

Clinical outcomes data with EPA

- Background to REDUCE IT: JELIS
- REDUCE IT main results
- Safety of IcosaPentEthyl
- **REDUCE IT ACS**

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.

Atrial Fibrillation / Flutter in Patients with Recent ACS <12 Months

	Icosapent Ethyl (N=433)	Placebo (N=407)	Overall (N=840)	P-value
	n (%)	*n (%)*	*n (%)*	
Atrial Fibrillation / Flutter TEAEs [1]	32 (7.4)	12 (2.9)	44 (5.2)	0.005
Serious Atrial Fibrillation / Flutter TEAEs [1]	5 (1.2)	3 (0.7)	8 (1.0)	0.73
Positively Adjudicated Atrial Fibrillation / Flutter Endpoints Requiring ≥24 Hours Hospitalization [2]	21 (4.8)	7 (1.7)	28 (3.3)	0.01

TEAE=Treatment-emergent adverse effect.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Adverse AF events, exclusive of positively adjudicated AF endpoints. P-value is based on Fisher's Exact test.
[2] P-value is based on stratified log-rank test.

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.

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Note: Hemorrhagic stroke is an adjudicated endpoint.

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

Clinical outcomes data with EPA

- Background to REDUCE IT: JELIS
- REDUCE IT main results
- Safety of Icosapent Ethyl
- REDUCE IT ACS
- **RESPECT EPA**

AHA 2022 Scientific Session Late-Breaking Clinical Trial
November 6, 2022

Randomized trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy - Statin and Eicosapentaenoic Acid (RESPECT-EPA)

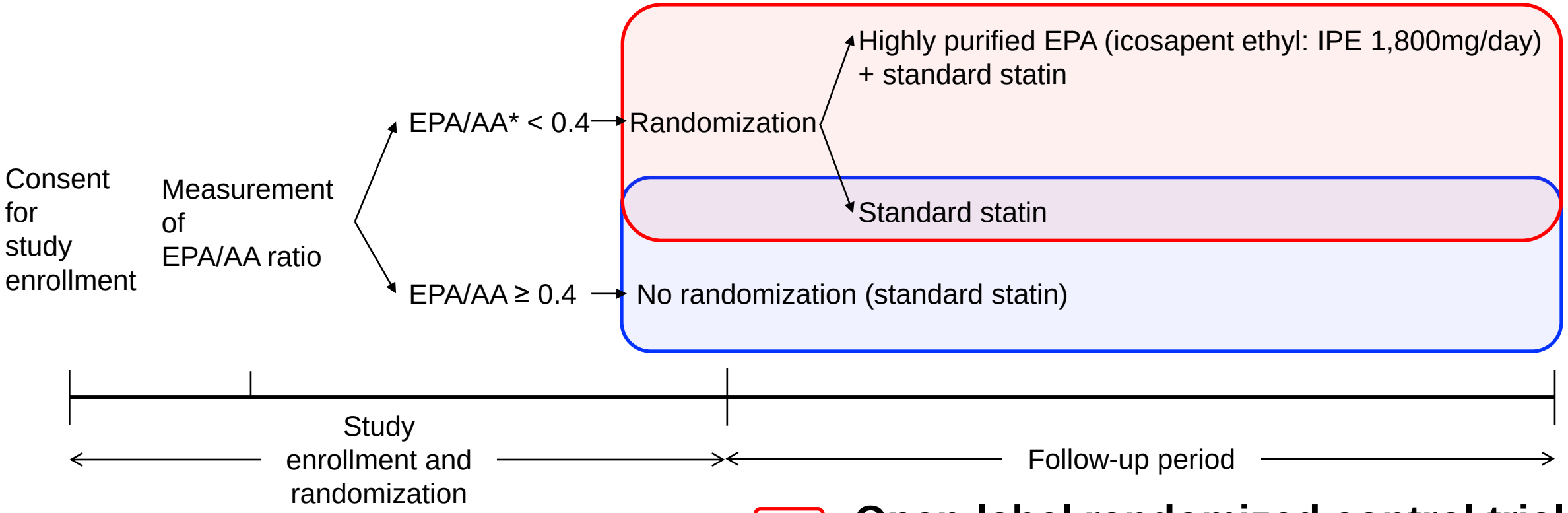
Hiroyuki Daida, Yuji Nishizaki, Hiroshi Iwata, Teruo Inoue, Atsushi Hirayama, Kazuo Kimura, Yukio Ozaki, Toyoaki Murohara, Kenji Ueshima, Yoshihiro Kuwabara, Sachiko Tanaka-Mizuno, Naotake Yanagisawa, Tosiya Sato, Katsumi Miyauchi

and RESPECT-EPA investigators

Supported by: Japan Heart Foundation

公益財団法人
日本心臓財団

Trial Scheme



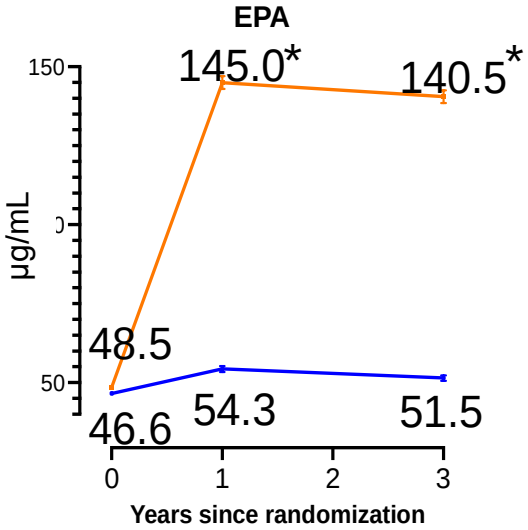
: Open-label randomized control trial

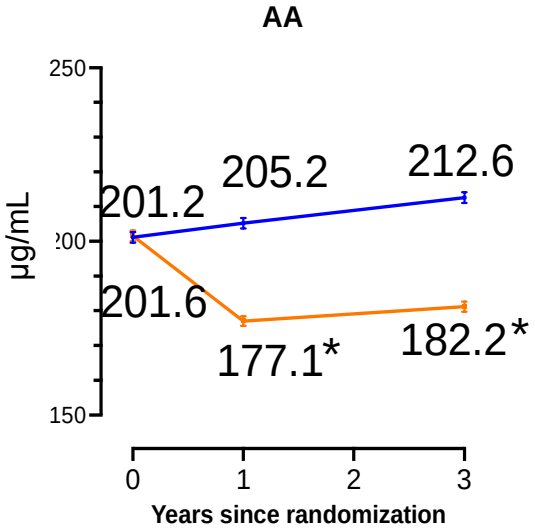
: Biomarker observational study

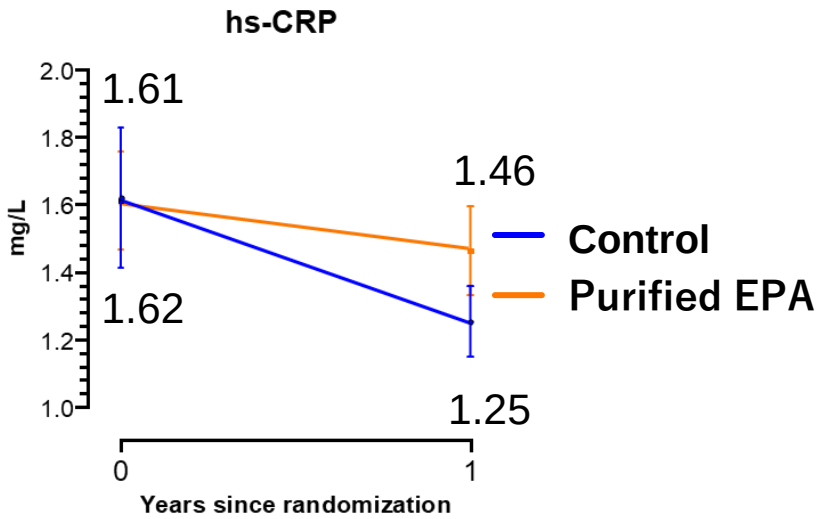
- Enrollment period: 4 years from November 1, 2013
- Follow-up period: 4 years from the end of the enrollment period

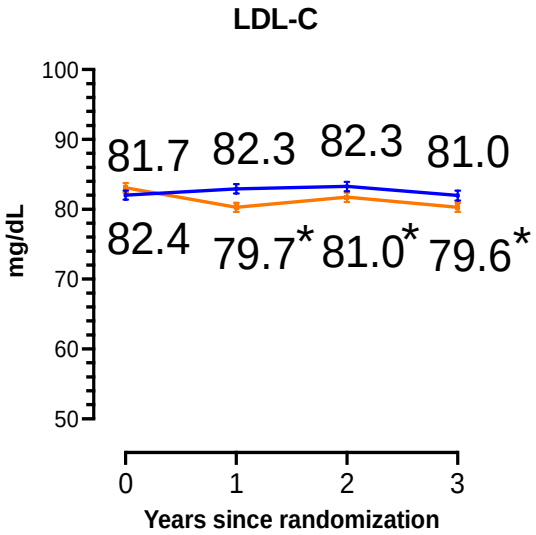
*EPA/AA: ratio of plasma eicosapentaenoic acid/ arachidonic acid

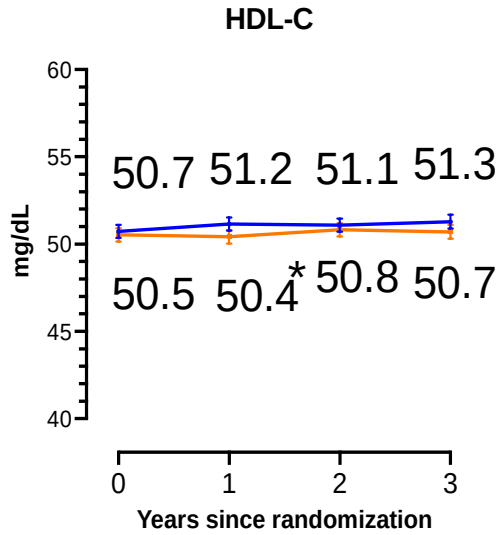
Changes in Fatty Acids, Lipid and hs-CRP

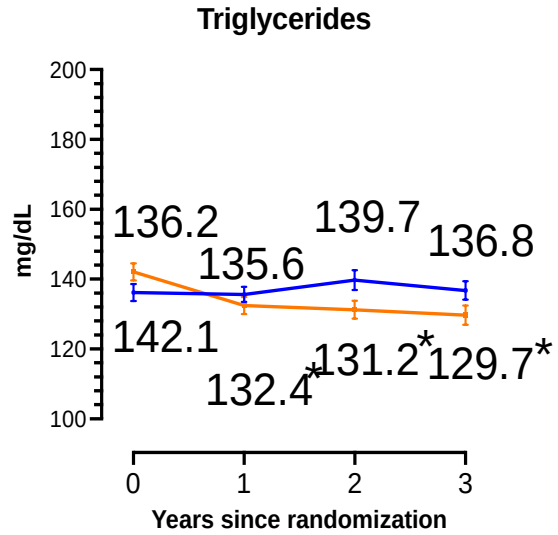








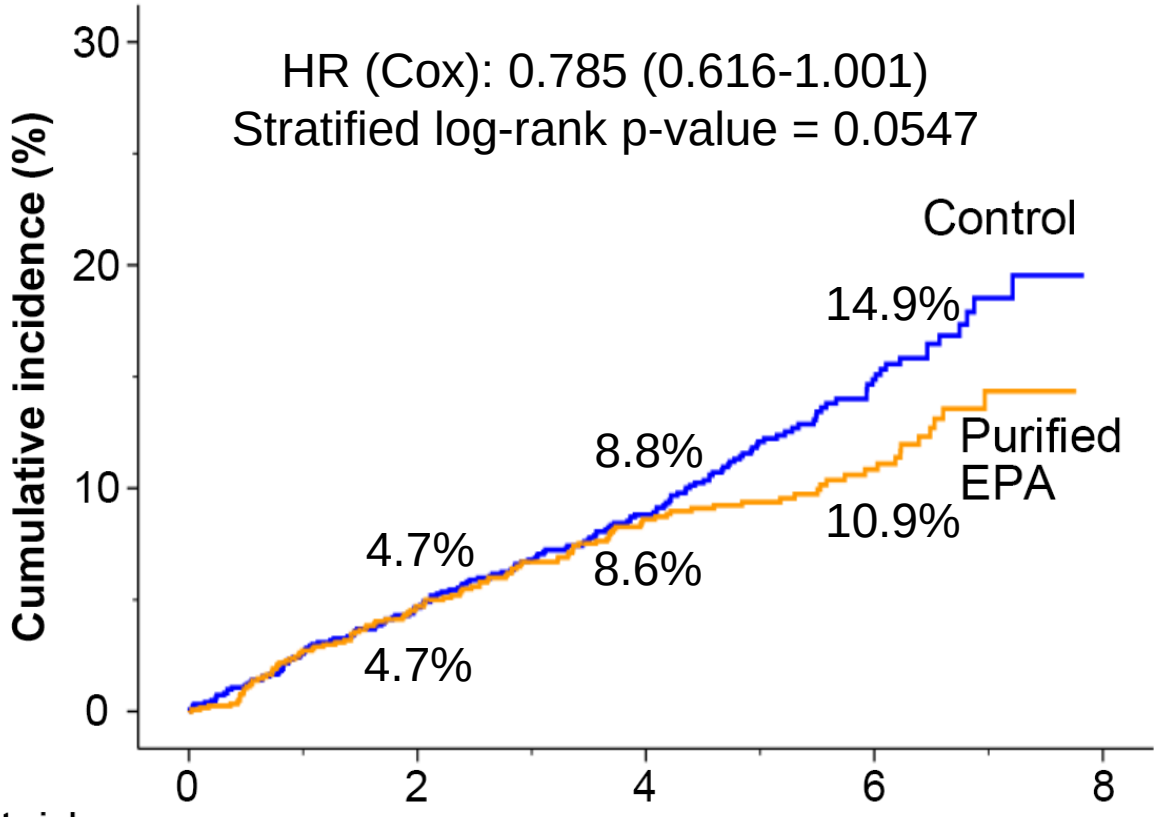




*: p<0.05 compared to baseline level by analysis of covariance

Primary and Secondary Endpoints

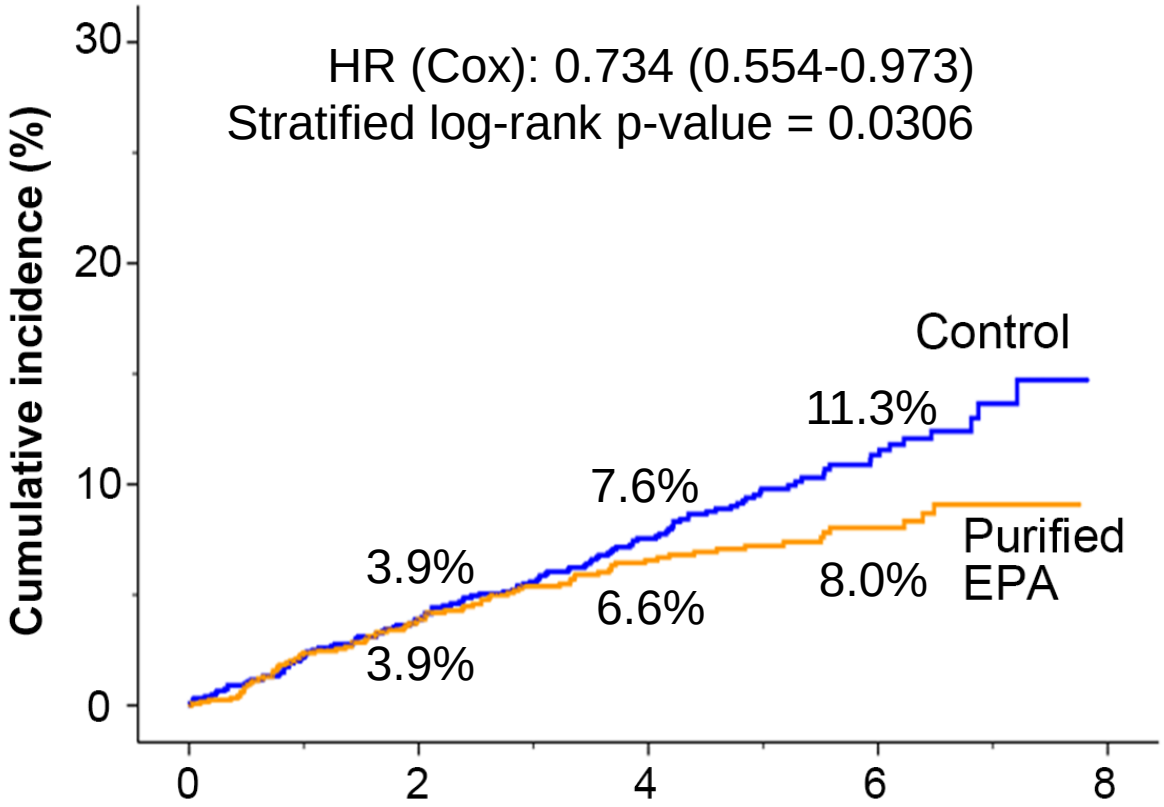
Primary Endpoint*



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**

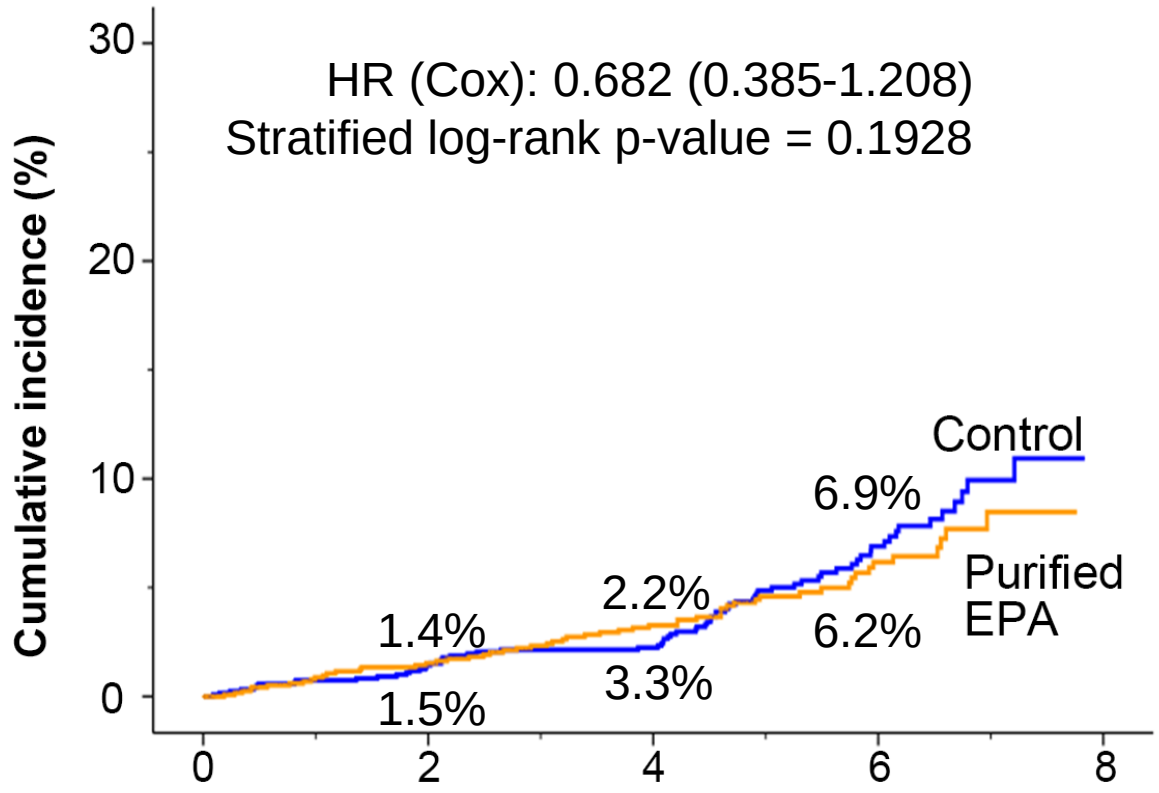


No. at risk				
Control	1235	1093	913	387
Purified EPA	1225	988	801	355

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

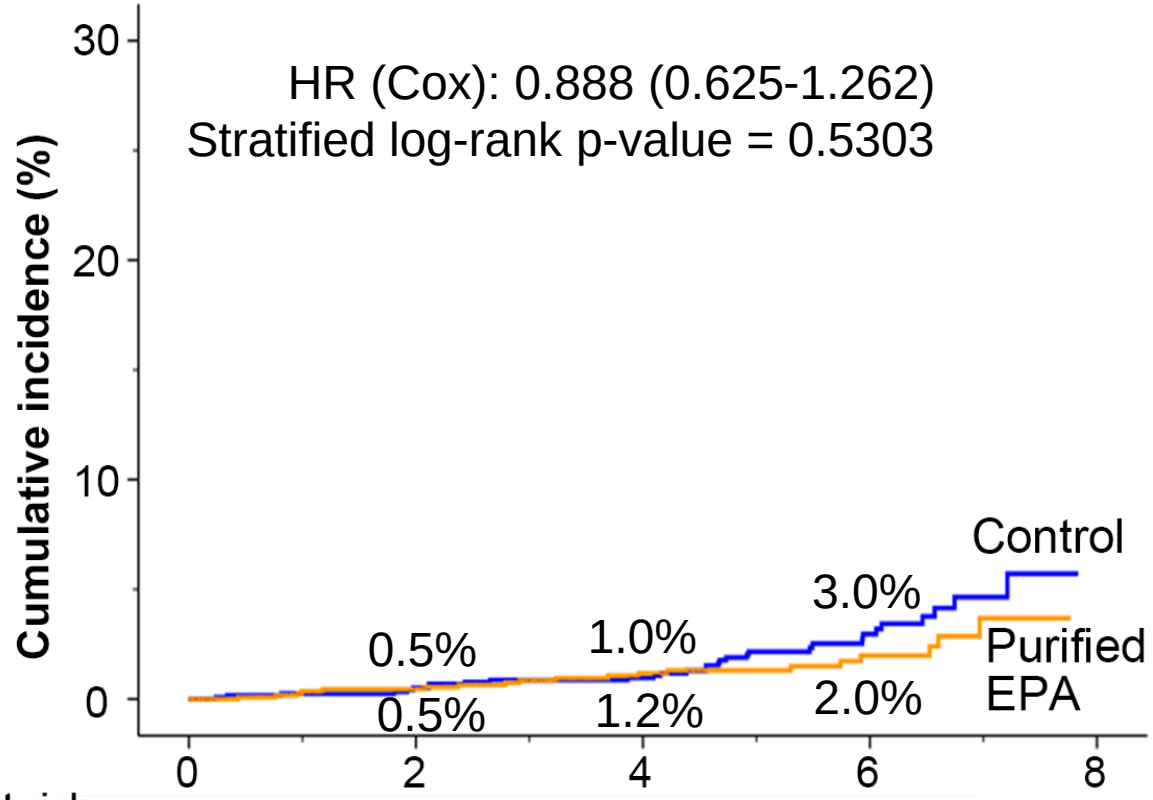
All-cause and Cardiovascular mortality

All-cause Mortality



No. at risk				
Control	1235	1129	976	432
Purified EPA	1225	1013	842	374

Cardiovascular Mortality



No. at risk				
Control	1235	1129	975	432
Purified EPA	1225	1015	844	375

Safety Outcomes

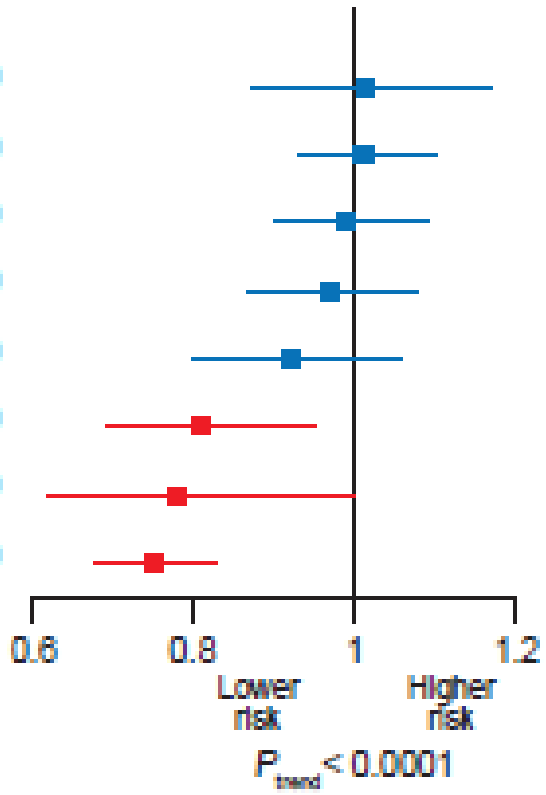
Events	Purified EPA group (N = 1225)	Control group (N = 1235)	P value
Gastrointestinal disorders, n (%)	42 (3.4%)	15 (1.2%)	<0.001
TIMI Bleeding, n(%)	27 (2.2%)	32 (2.6%)	0.599
Major	13 (1.1%)	15 (1.2%)	0.850
Minor/Minimum	14 (1.1%)	17 (1.4%)	0.718
New-onset diabetes mellitus, n(%)	26 (2.1%)	15 (1.2%)	0.085
Low density lipoprotein increase, n(%)	22 (1.8%)	31 (2.5%)	0.267
Liver enzyme elevation, n(%)	8 (0.7%)	13 (1.1%)	0.381
New-onset atrial fibrillation	38 (3.1%)	20 (1.6%)	0.017

Clinical outcomes data with EPA

- Background to REDUCE IT: JELIS
- REDUCE IT main results
- REDUCE IT ACS
- Safety of Icosapent Ethyl
- RESPECT EPA
- **Contrasting trial results of EPA vs EPA+DHA trials**

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)



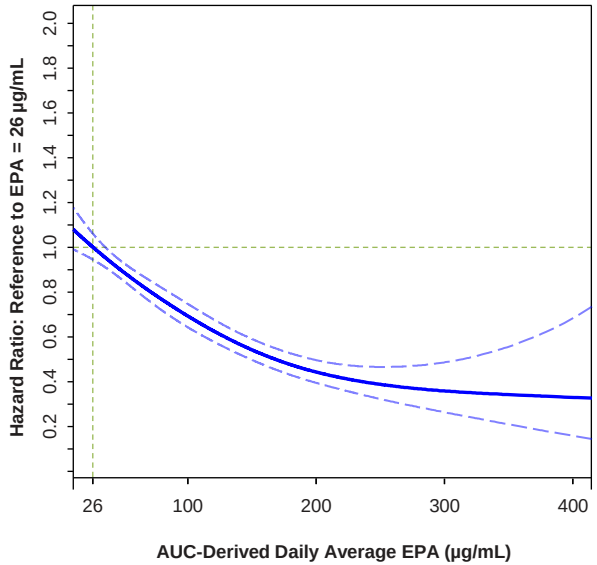
The benefit is highly correlated to on-treatment EPA levels

Dose-Response of Hazard Ratio (95% CI)

Primary Composite Endpoint by On-Treatment Serum EPA

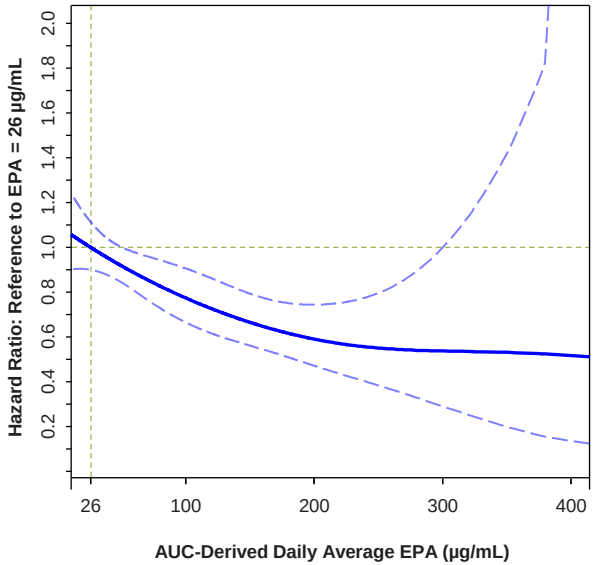
Established Cardiovascular Disease or Diabetes with Risk Factors

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

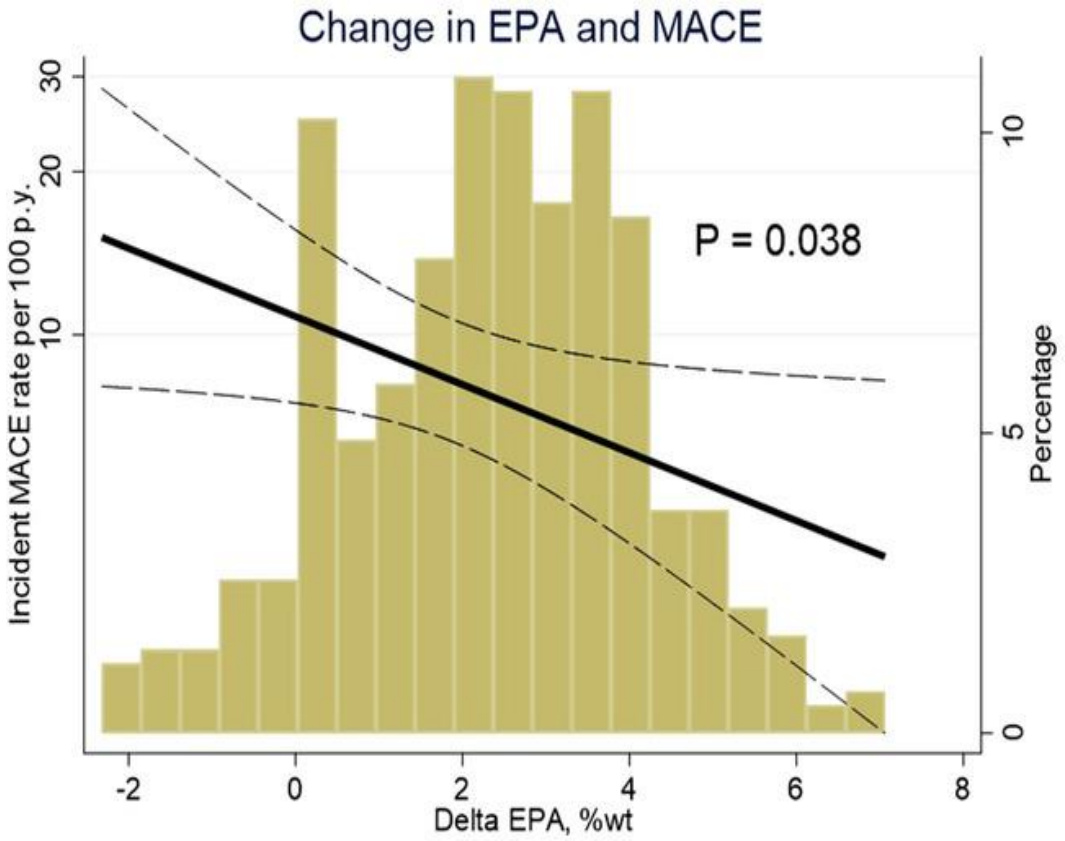
Dose-response hazard ratio — 95% Confidence Interval (CI) - - -

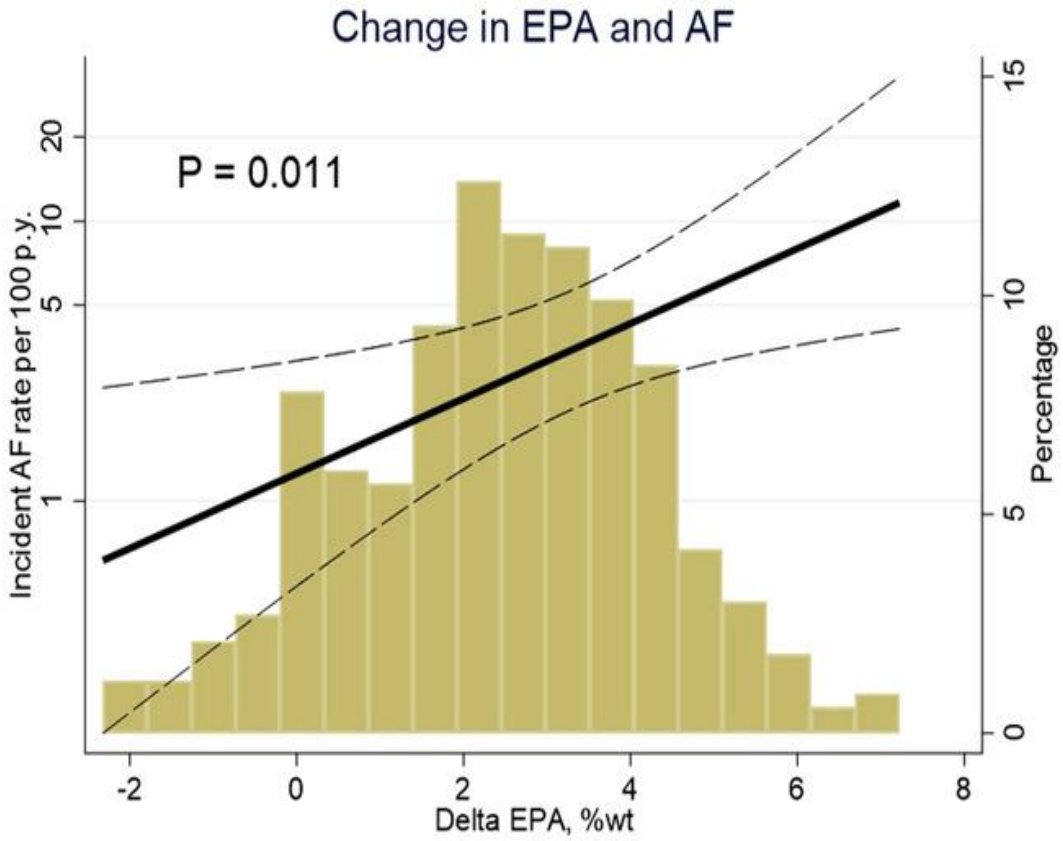
P*<0.001 for all

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).

Changes in EPA and risk of cardiovascular events and atrial fibrillation: A secondary analysis of the OMEMI trial

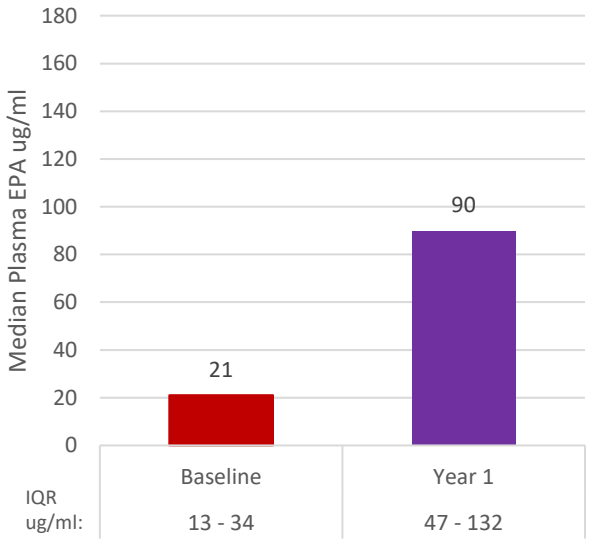




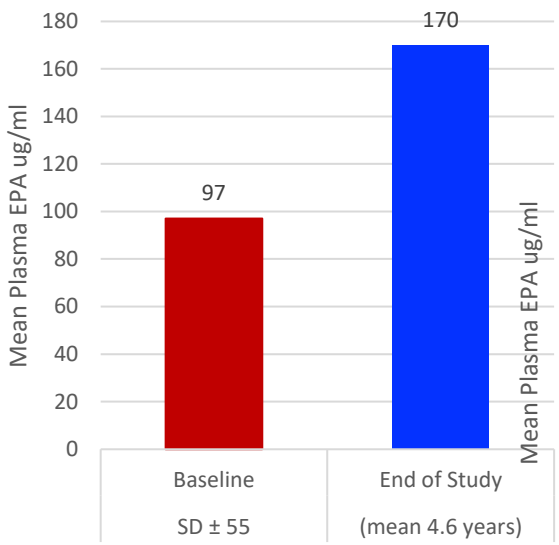
Myhre PL et al. ***Journal of Internal Medicine,*** 2022: 291: 637-647

Baseline and Achieved EPA Levels in Omega-3 CVOTs Cross-study Comparison

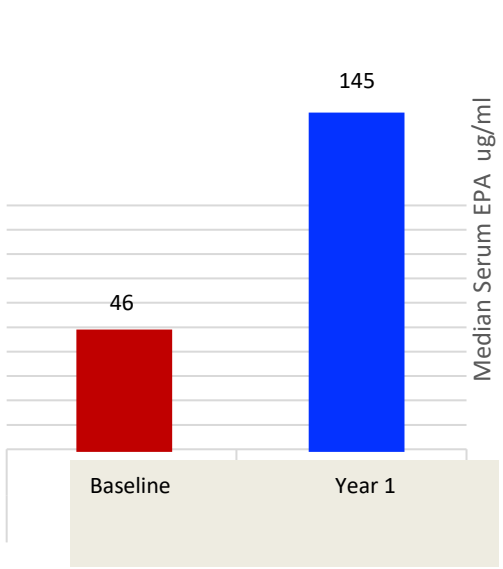
STRENGTH[1]
Plasma EPA



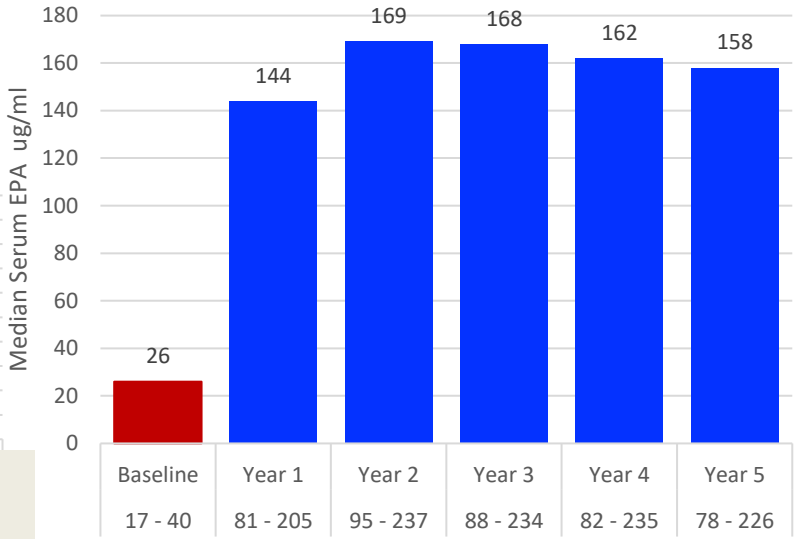
JELIS[2]
Plasma EPA



RESPECT EPA[4]
Plasma EPA



REDUCE-IT[3]
Serum EPA



Drug:	850 mg mixed omega-3 carboxylic acid / 1g capsule	>980 mg EPA ethyl ester / 1g capsule	1g icosapent ethyl (EPA ethyl ester) / 1g capsule
Dose:	4 g/d	1.8 g/d	4 g/d
Population:	International	Japanese	International

Plasma and serum EPA levels have been strongly correlated, with plasma levels being slightly higher than serum levels[4,5]

1. Nicholls SJ, et al. *JAMA*. 2020 Nov 15:e2022258 2. Itakura H, et al. *J Atheroscler Thromb*. 2011;18:99–107. 3. Bhatt DL, et al. ACC 2020 Scientific Session (ACC.20)/World Congress of Cardiology (WCC): Abstract 20-LB-20501-ACC. Presented March 30, 2020. 4. Dunbar RL, et al. Poster presented at the Gordon Conference on Atherosclerosis, June 16-21, 2019, Newry, Maine. 5. Dunbar, RL, et al. poster presented at NLA Scientific Sessions, Dec 9-12, 2020.

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
- Benefit appears strongly correlated to achieved EPA levels, (but not to TGs, LDL-C, or hs-CRP)