PLACE 2026
PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

CONGRESSO
ROMA, 25 - 27 Giugno 2026

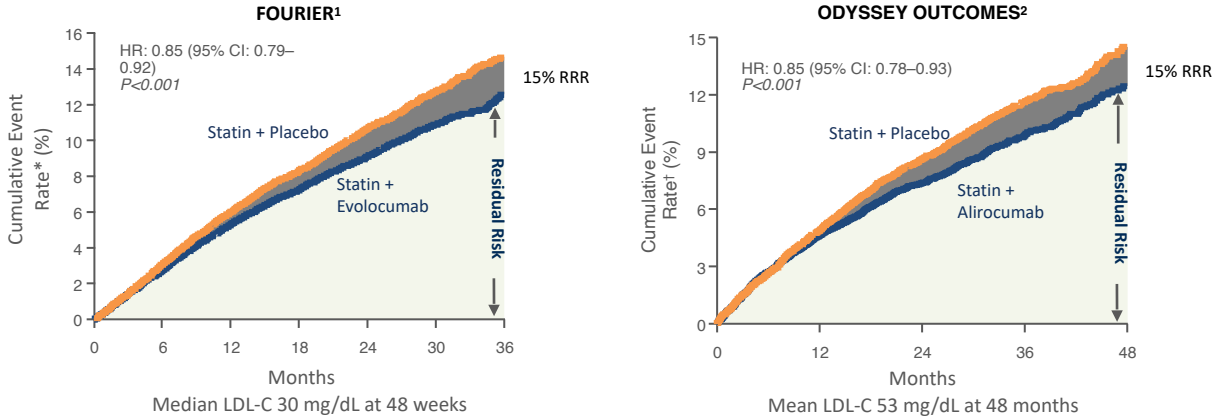
FOCUS ON DISLIPIDEMIE E PREVENZIONE CARDIOVASCOLARE

Oltre il colesterolo LDL: lo studio Reduce IT

Prof Alberto Corsini
Università degli Studi di Milano

Dichiaro che negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario

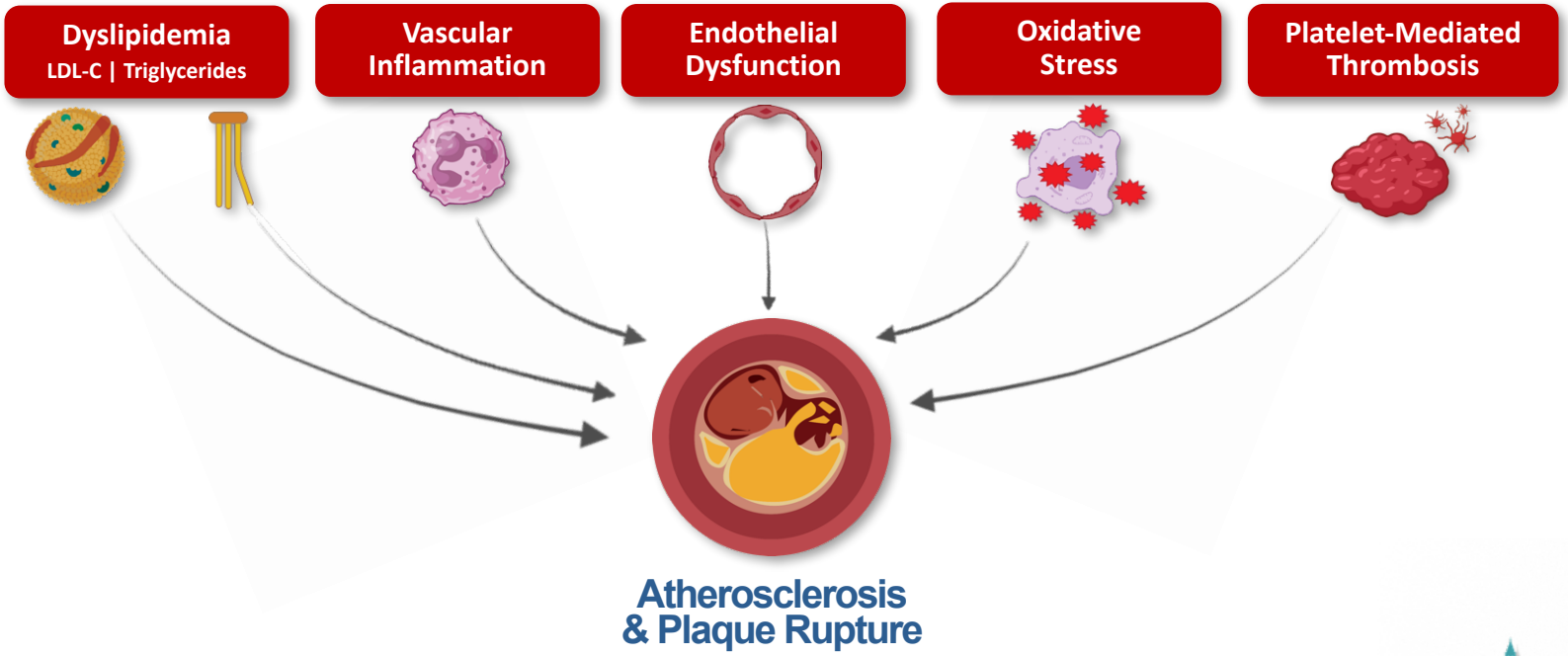
- AMGEN
- Sanofi
- Novartis
- MSD
- Organon
- Amarin
- Servier
- Daiichi Sankyo
- DOC
- Fidia
- PIAM
- Viatris
- CSL Vifor
- Menarini



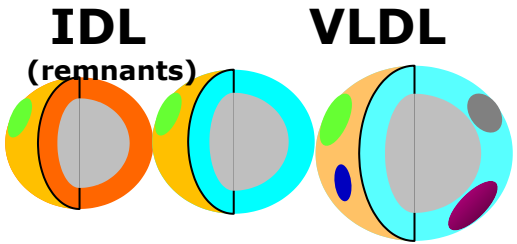
*Composite of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation[1]; †Composite of death due to coronary heart disease, non-fatal MI, fatal or non-fatal ischaemic stroke or hospitalisation for unstable angina.[2]

CI: confidence interval; HR: hazard ratio; FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; LDL-C: low density lipoprotein-cholesterol; MI: myocardial infarction; ODYSSEY-OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PCSK9:Proprotein convertase subtilisin/kexin type 9; RRR: relative risk reduction.

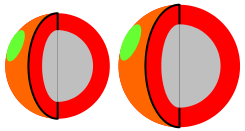
Elevated LDL-C is only one of *multiple pathophysiologic factors* that drive progression of atherosclerosis and plaque rupture



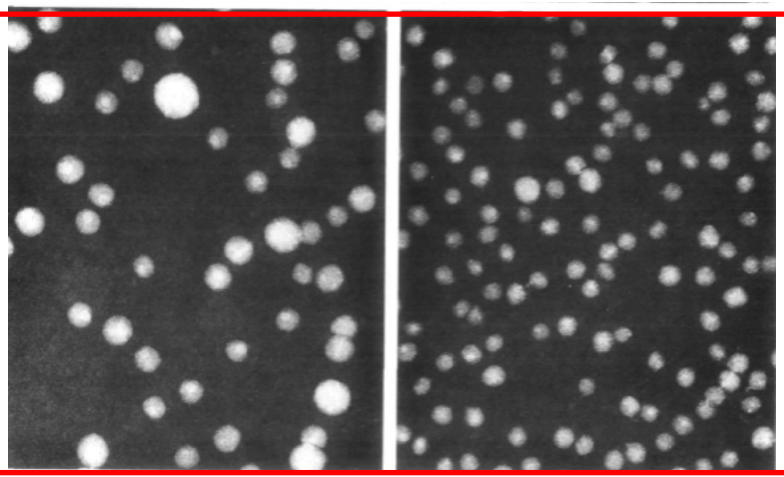
Bae JH, et al. *Advances in Nutrition.* 2023. https://doi.org/10.1016/j.advnut.2023.03.014



ATHEROSCLEROTIC
CORONARY PLAQUE EXTRACTS



….**VLDL+IDL** accounting for **36%** of the lipoprotein **cholesterol** from the atherosclerotic plaque extracts….



Photomicrographs show negatively stained lipoproteins from a single patient:
Left pictures show very-low-density lipoprotein+ intermediate-density lipoprotein;
Right pictures, low-density lipoprotein.

Havel RJ, Kane JP et al Arterioscler Thromb. **1994**;14:1767-1774.

ESC European Heart Journal (2026) 00, 1–19
https://doi.org/10.1093/eurheartj/ehag087

Residual lipid risk in atherosclerotic cardiovascular disease

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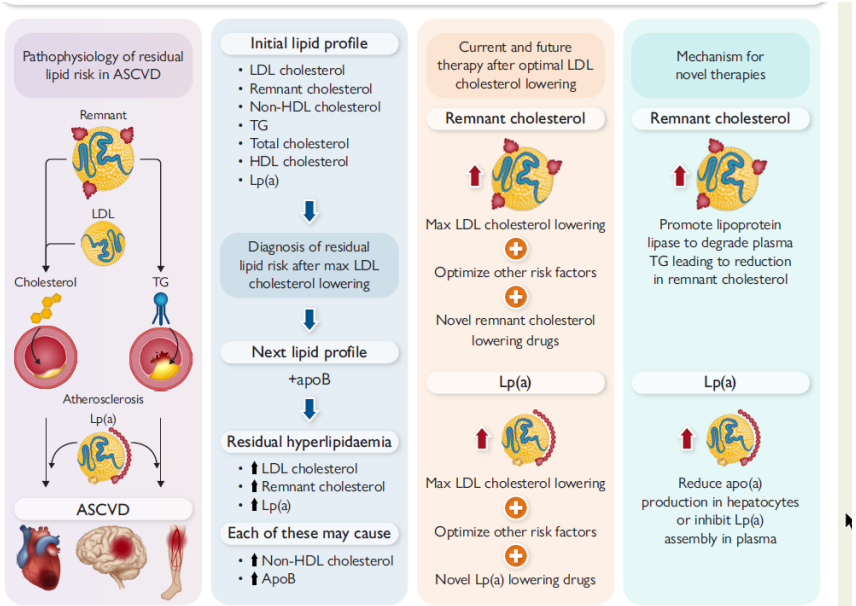
Received 24 August 2025; revised 28 October 2025; accepted 24 January 2026



Apo(a), apolipoprotein(a); **ApoB**, apolipoprotein B; **ASCVD**, atherosclerotic cardiovascular disease; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **Lp(a)**, lipoprotein(a); **TG**, triglycerides

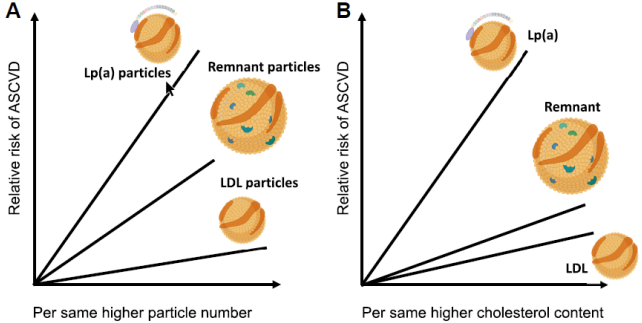
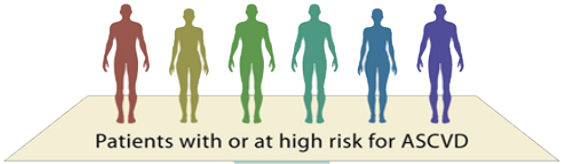


Figure 2 Atherosclerotic cardiovascular disease by the same increase in particle numbers and cholesterol content for different lipoproteins. (*A*) Relationship between particle number and ASCVD risk for LDL, remnants and Lp(a); (*B*) Relationship between cholesterol content of each particle species and ASCVD risk. Figure created partly using Biorender. ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; Lp(a), lipoprotein(a). Adapted from references [42–47]

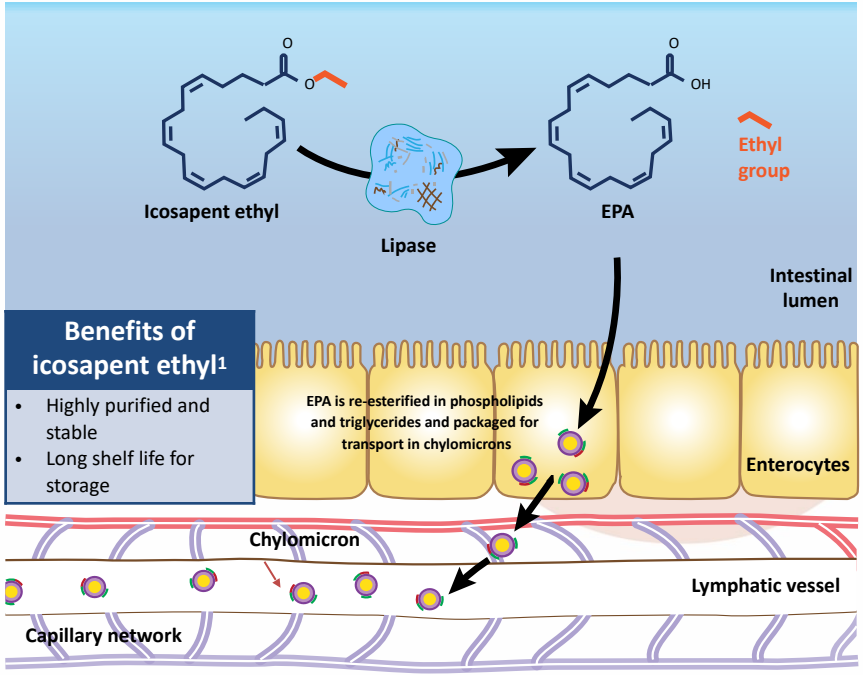
Icosapent ethyl addresses the TG component of residual risk



Optimal LDL-C levels

Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

ICOSAPENT ETHYL

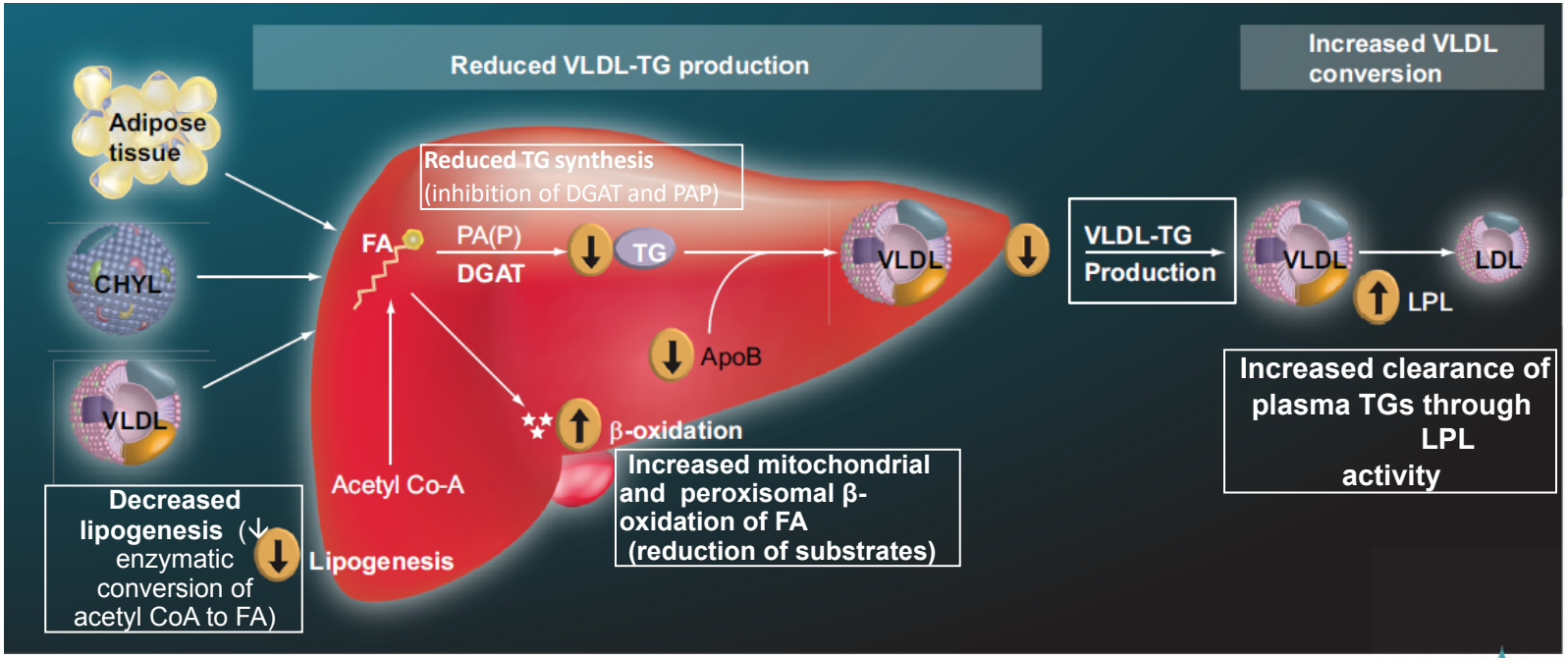


Adapted from: Wang X, et al. *Curr Diab Rep.* 2020;20(11):65.[1]

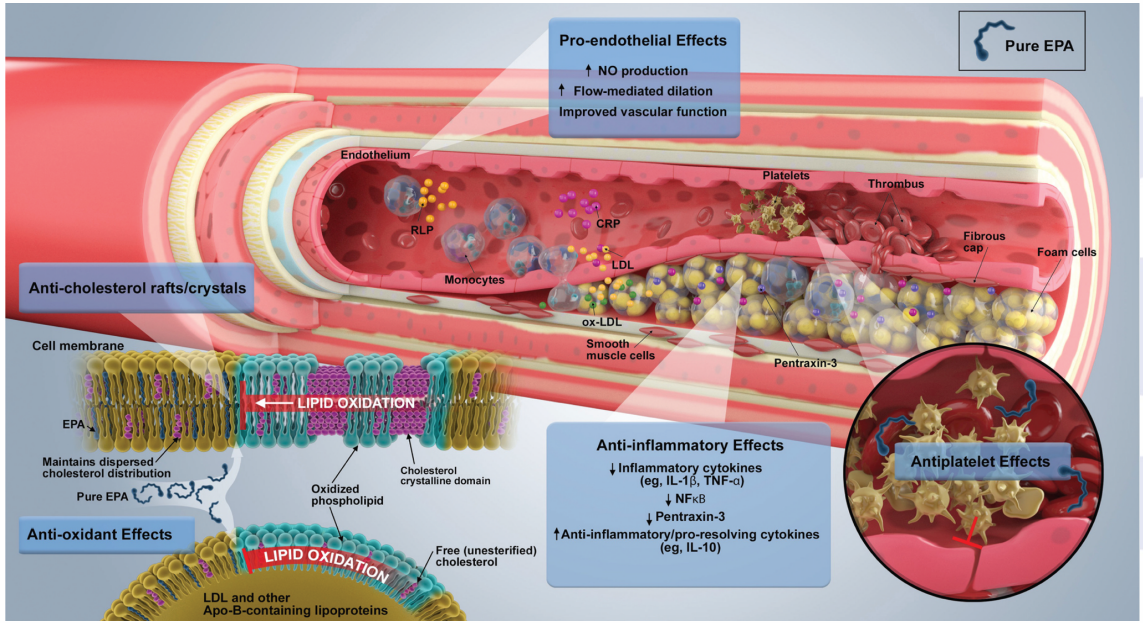
- Addition of ethyl ester enables:[2]
  - Greater purification
  - Higher concentration
  - Higher stability
  - Longer shelf life
- Icosapent ethyl is de-esterified to EPA in the small intestine and absorbed[2]
- Once absorbed, EPA is transported in blood inside chylomicrons.[2]
- Peak plasma concentrations of EPA ~5 hours.[2]
- 99% bound to plasma proteins.[2]
- Plasma elimination $t_{1/2}$ = 89 hours.[2]
- Elimination is by hepatic metabolism.[2]
- Does not undergo renal excretion.[2]

EPA, eicosapentaenoic acid; t½, half-life

- Reducing VLDL production and secretion
- Increasing VLDL metabolism



CHYL: Chylomicrons; DGAT, diacylglycerol acyltransferase; FA, fatty acid; LDL, low-density lipoprotein; Co A, coenzyme A; PAP, phosphatidic acid phosphatase/phosphohydrolase; TG, triglyceride; VLDL, very low-density lipoprotein; LPL: Lipoprotein lipase.



EPA INCREASES

- Fibrous cap thickness
- Lumen diameter
- Plaque stability

EPA DECREASES

- Plaque volume
- Arterial stiffness
- Plaque vulnerability
- Thrombosis
- Platelet activation

AA: arachidonic acid; CRP: C-reactive protein; EPA: eicosapentaenoic acid; hsCRP: high-sensitivity C-reactive protein; ICAM-1: intercellular adhesion molecule 1; IL-6: interleukin 6; IL-10: interleukin 10; LDL: low-density lipoprotein; Lp-PLA_2: lipoprotein-associated phospholipase A; oxLDL: oxidised low-density lipoprotein; RLP-C: remnant lipoprotein cholesterol.

Miller M, et al. EXPERT REVIEW OF CARDIOVASCULAR THERAPY *2022*;

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Bhatt DL et al. *N Engl J Med.* 2019;380(1)

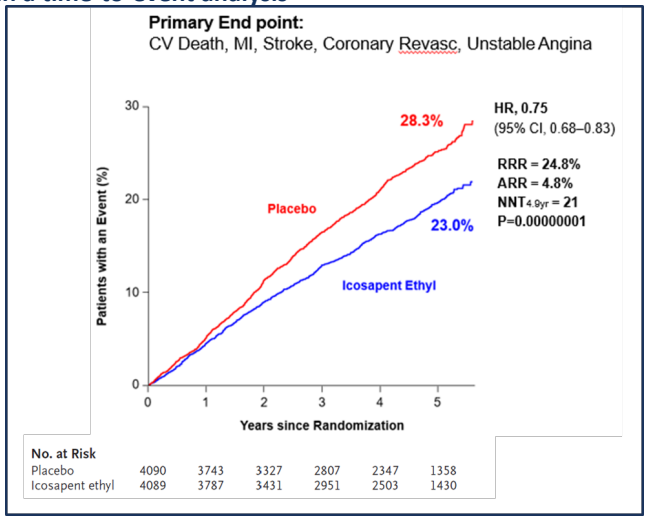
Baseline characteristics were similar between treatment groups

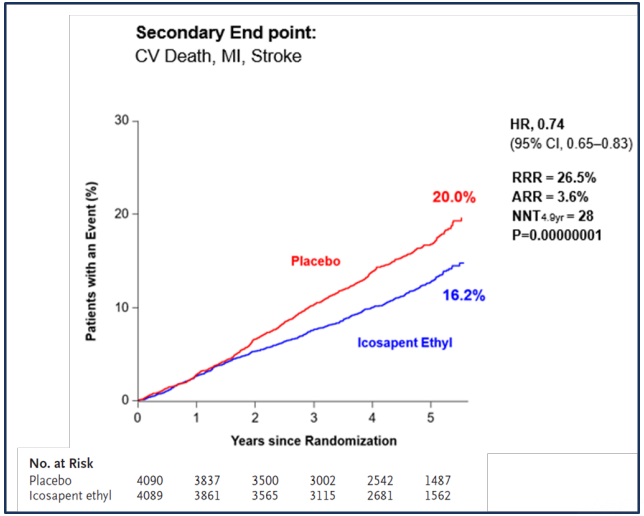
Parameter		Icosapent ethyl 4 g/day (n=4089)	Placebo (n=4090)
Median Age (years)		64.0	64.0
Female (%)		28.4%	29.2%
CV Risk Category (%)	Secondary Prevention Cohort	70.7%	70.7%
	Primary Prevention Cohort	29.3%	29.3%
Type 2 Diabetes (%)		57.9%	57.8%
Ezetimibe Use, n (%)		6.4%	6.4%
Statin Intensity (%)	Low	6.2%	6.5%
	Moderate	61.9%	63.0%
	High	31.5%	30.0%
Medication Taken at Baseline[2]	Antihypertensive	95.3%	95.2%
	Antiplatelet	79.7%	79.1%
	Antidiabetic	53.6%	53.7%
	Anticoagulant	9.4%	9.5%
Triglycerides (mg/dl), median		216	216
Triglycerides Category	< 150 mg/dl	10.1%	10.5%
	150 to < 200 mg/dl	29.2%	29.1%
	≥200 mg/dl	60.7%	60.4%
LDL-C (mg/dl)		74	76
HDL-C (mg/dl)		40	

1. Bhatt DL, et al. *N Engl J Med*. 2019;380(1). **2**. Bhatt DL et al. *J Am Coll Cardiol*. 2019;73(22).

Primary and key secondary endpoints

Cumulative incidence for the primary and secondary efficacy composite end point in the 2 trial groups in a time-to-event analysis

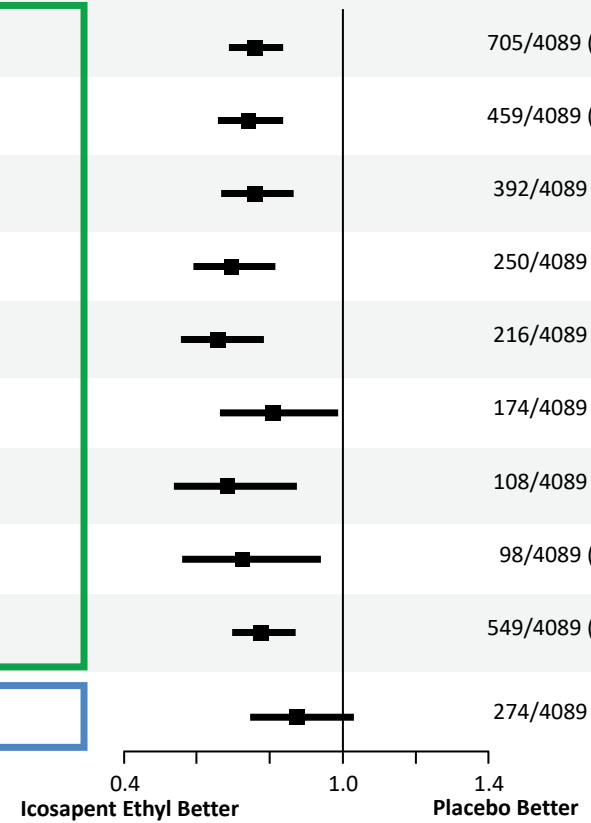




ARR, absolute risk reduction; HR, hazard ratio; MACE, major adverse cardiovascular event; NNT, number needed to treat; RRR, relative risk reduction.

Bhatt DL et al. *N Engl J Med.* 2019;380(1).

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 [illegible]

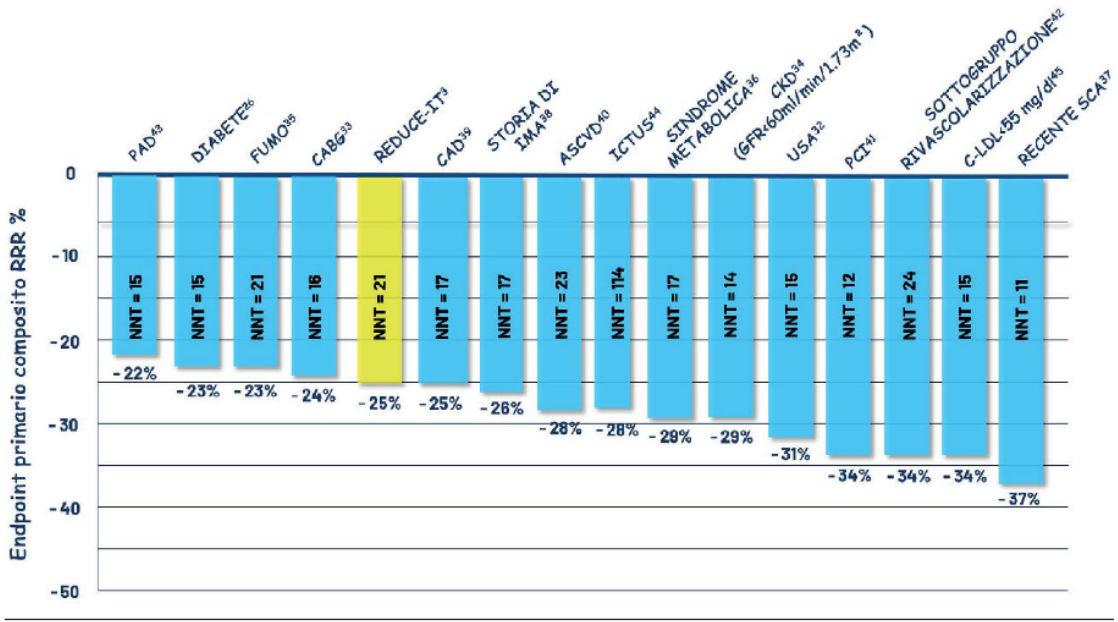


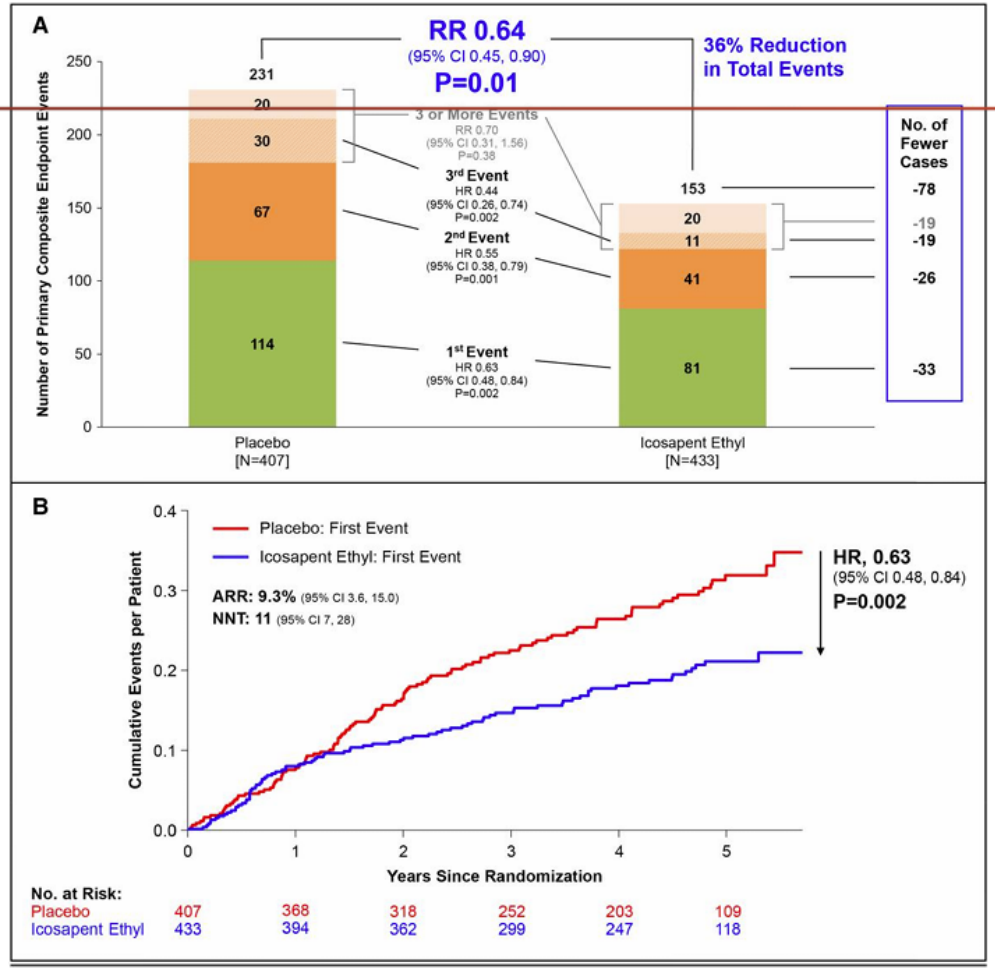
Figura 1. Risultati delle principali sottoanalisi del trial REDUCE-IT rispetto al trial complessivo.
ASCVD, malattia cardiovascolare aterosclerotica; CABG, bypass aortocoronarico; CAD, malattia coronarica; CKD, malattia renale cronica; C-LDL, colesterolo legato alle lipoproteine a bassa densità; GFR, velocità di filtrazione glomerulare; IMA, infarto miocardico acuto; NNT, number needed to treat; PAD, arteriopatia periferica; PCI, procedura coronarica percutanea; RRR, riduzione del rischio relativo; SCA, sindrome coronarica acuta.

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 1173–1176
https://doi.org/10.1093/eurheartj/ehad889

RAPID COMMUNICATIONS
Clinical trials

Icosapent ethyl following acute coronary syndrome: the REDUCE-IT trial

Neila Sayah [1]*, Deepak L. Bhatt [2], Michael Miller [3], Eliot A. Brinton [4], Terry A. Jacobson [5], Steven B. Ketchum [6], Lixia Jiao [6], Armando Lira Pineda [6], Ralph T. Doyle Jr. [6], Jean Claude Tardif [7], Christie M. Ballantyne [8], and Ph. Gabriel Steg [1,9]; on behalf of the REDUCE-IT Investigators†



European Heart Journal
(2024) 45, 1173–1[illegible]6

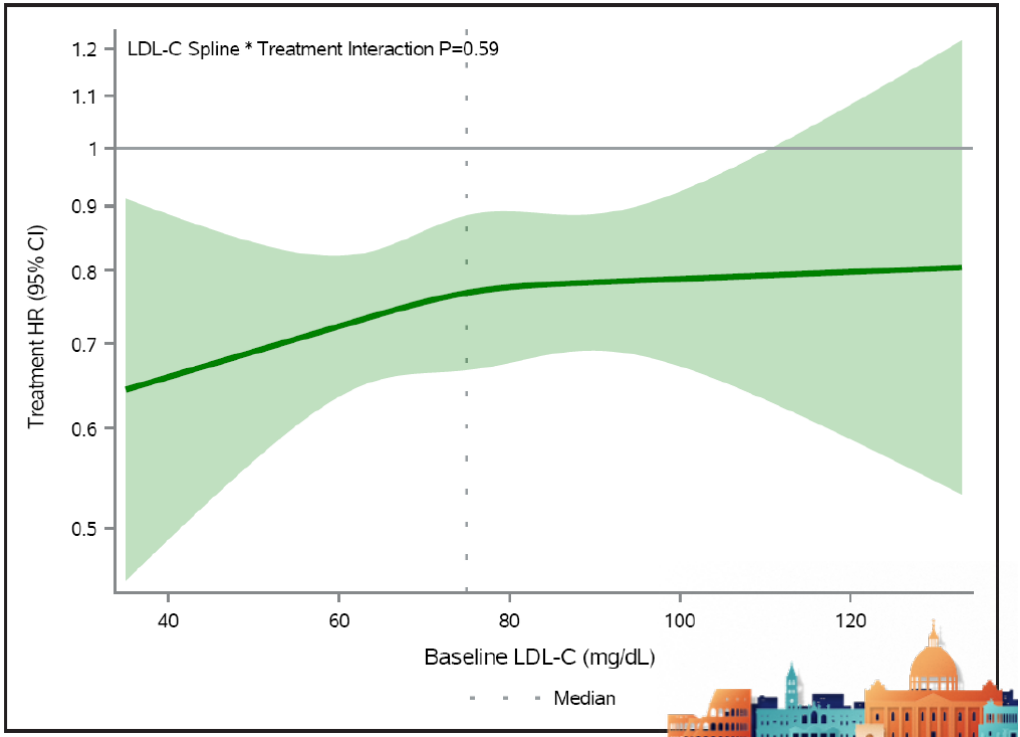
EFFICACY OF ICOSAPENT ETHYL BY BASELINE LDL-C

Journal of the American Heart Association

ORIGINAL RESEARCH

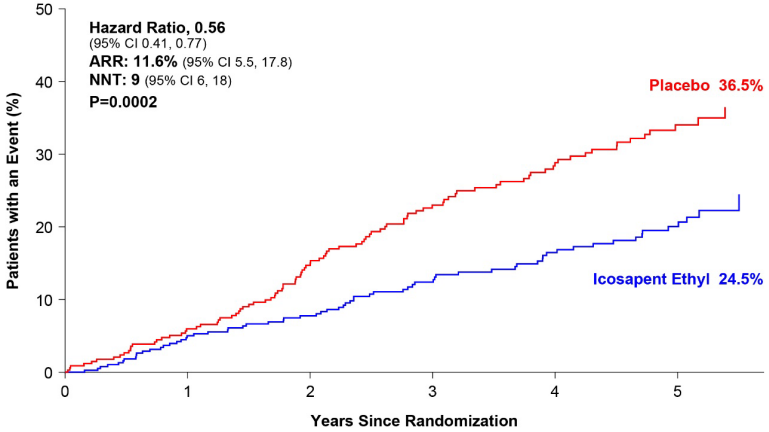
Cardiovascular Outcomes With Icosapent Ethyl by Baseline Low-Density Lipoprotein Cholesterol: A Secondary Analysis of the REDUCE-IT Randomized Trial

Rahul Aggarwal, MD; Deepak L. Bhatt, MD, MPH, MBA; Ph. Gabriel Steg, MD; Michael Miller, MD; Eliot A. Brinton, MD; Richard L. Dunbar, MD, MSTR; Steven B. Ketchum, PhD; Jean-Claude Tardif, MD; Fabrice M. A. C. Martens, MD, PhD; Christie M. Ballantyne, MD; Michael Szarek, PhD; R. Preston Mason, PhD, MBA; on behalf of REDUCE-IT Investigators†



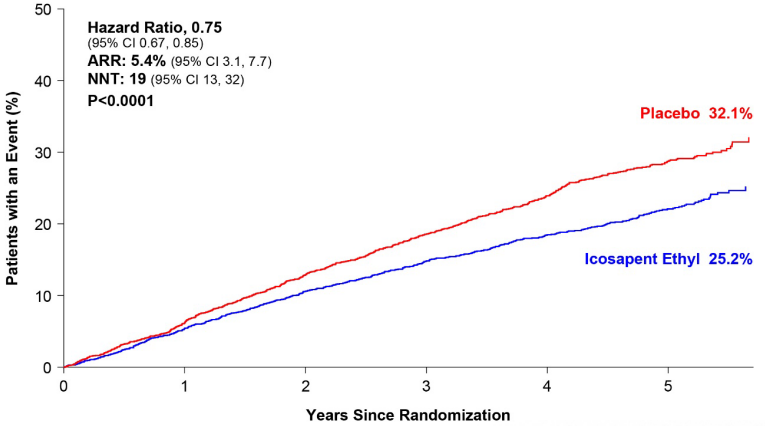
KAPLAN MEIER PLOT OF PRIMARY COMPOSITE END POINT BY BASELINE LDL-C AMONG PATIENTS WITH CARDIOVASCULAR DISEASE HYSTORY

LDL-C< 55mg/dl (726)



No. at Risk:						
Placebo	339	309	263	198	161	86
Icosapent Ethyl	387	353	317	254	210	131

LDL-C ≥ 55mg/dl (5055)

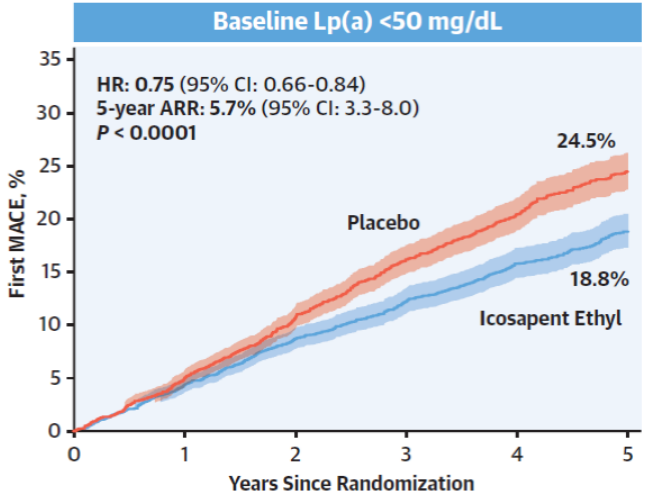


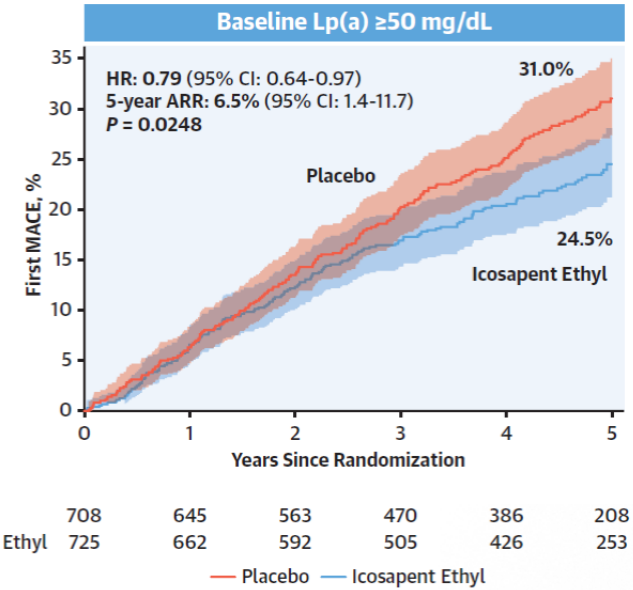
No. at Risk:						
Placebo	2553	2325	2051	1679	1352	763
Icosapent Ethyl	2502	2316	2078	1727	1428	786

J Am Heart Assoc. 2025;14:e038656. DOI: 10.1161/JAHA.124.038656

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 83, NO. 16, 2024

Lipoprotein(a) Blood Levels and Cardiovascular Risk Reduction With Icosapent Ethyl





Szarek M et al, JACC 2024

Effects on Biomarkers from Baseline to Year 1

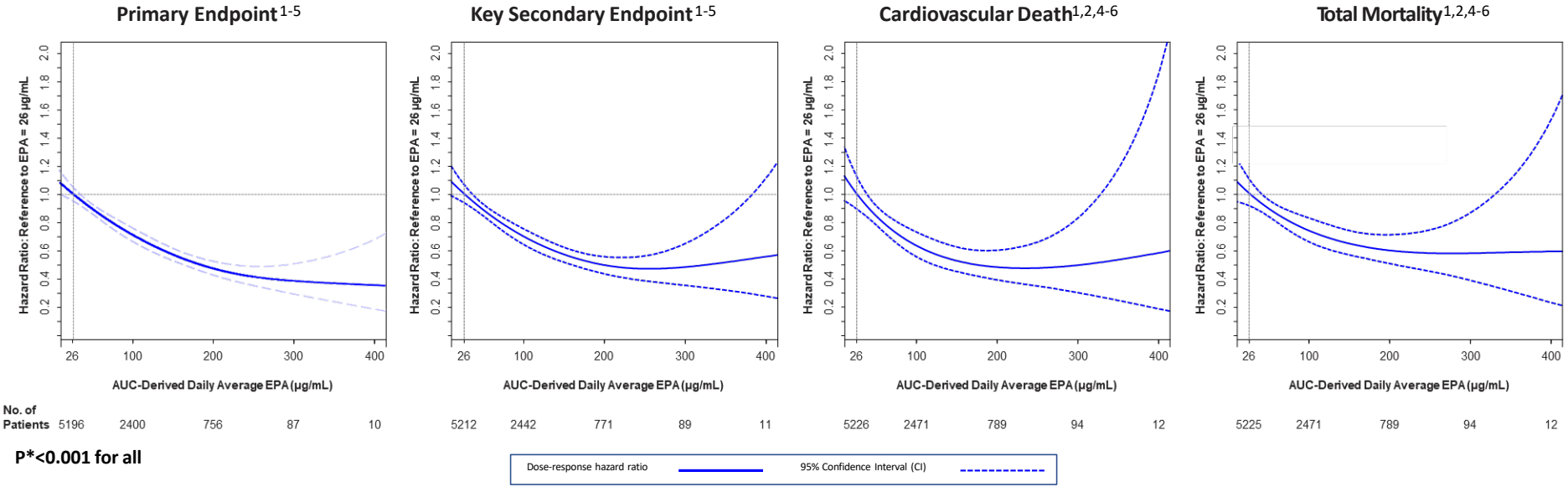
reduce-it

	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.* 2018.

Dose-response of Hazard Ratio (95% CI) Primary and Secondary Endpoints, Cardiovascular Death and Total Mortality by On-Treatment Serum EPA



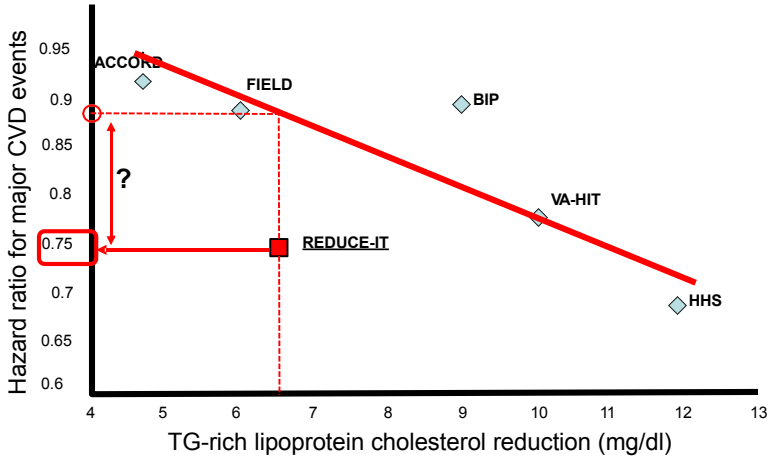
Note: Area under the curve (AUC)-derived daily average serum EPA (µg/mL) is the daily average of all available post baseline EPA measurements prior to the event. Dose-response hazard ratio (solid line) and 95% CI (dotted lines) are estimated from the Cox proportional hazard model with a spline term for EPA and adjustment for randomization factors and statin compliance[1], age[2], sex[3], baseline diabetes[4], hsCRP[5], treatment compliance[6].
*P value is <0.001 for both non-linear trend and for regression slope.

Bhatt DL. ACC/WCC 2020, Chicago (congress presentation).

Eicosapentaenoic Acid, Arachidonic Acid, and Triglyceride Levels Mediate Most of the Benefit of Icosapent Ethyl in REDUCE-IT

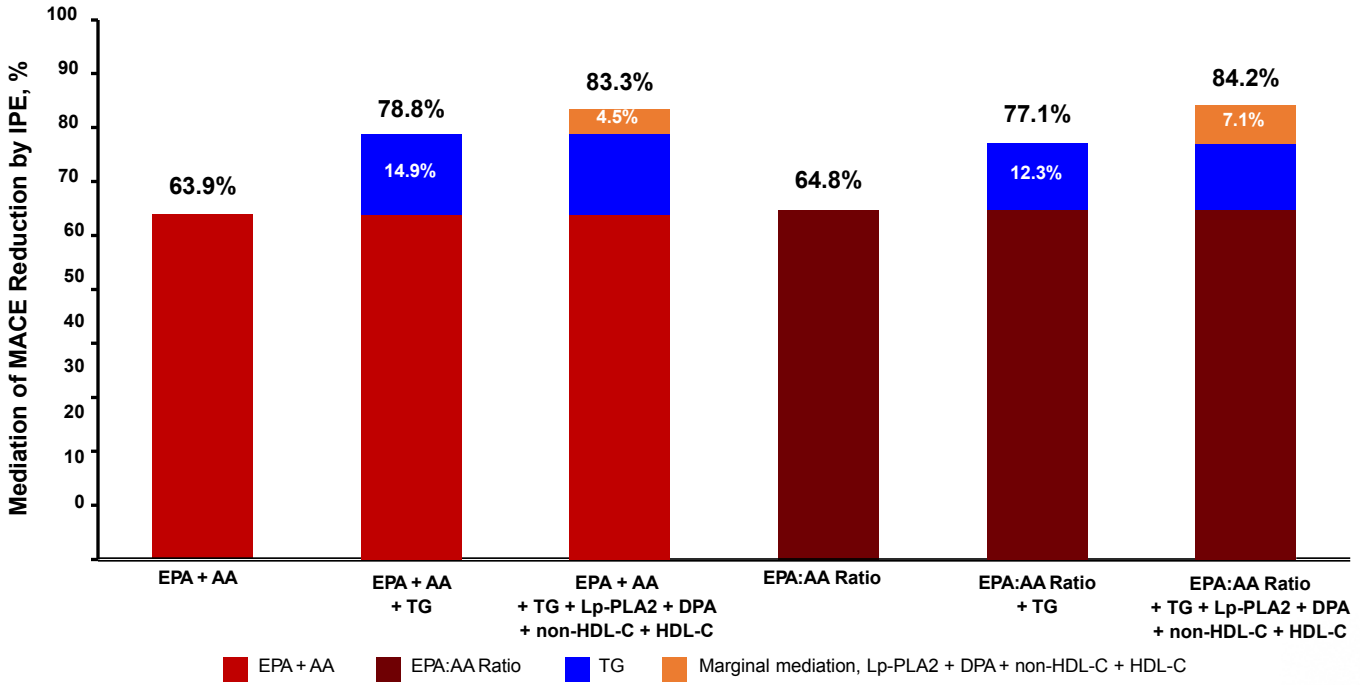
Michael Szarek Ph.D., **Deepak L. Bhatt, M.D., M.P.H.**, Michael Miller, M.D., Ph. Gabriel Steg, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Jean-Claude Tardif, M.D., Christie M. Ballantyne, M.D., Steven B. Ketchum, Ph.D., Armando Lira Pineda, M.D., Richard L. Dunbar, M.D., Patty W. Siri-Tarino, Ph.D., R. Preston Mason, Ph.D., on Behalf of the **REDUCE-IT** Investigators

Association between the magnitude of TG-rich lipoprotein cholesterol reduction and the risk of cardiovascular events in FIBRATE trials and REDUCE-IT



Current Atherosclerosis Reports, In press September 2020

Multivariate Mediation of IPE MACE Reduction



Szarek M, Bhatt DL, Miller M, et al., ESC 2023

New Recommendations (6)

ESC
EAS

Recommendations	Class	Level
Recommendations for drug treatment of patients with hypertriglyceridaemia		
High-dose icosapent ethyl (2 x 2 g/day) should be considered in combination with a statin in high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride levels 135–499 mg/dL or 1.52–5.63 mmol/L) to reduce the risk of cardiovascular events.	IIa	B
Volanesorsen (300 mg/week) should be considered in patients with severe hypertriglyceridaemia (>750 mg/dL or >8.5 mmol/L) due to familial chylomicronaemia syndrome, to lower triglyceride levels and reduce the risk of pancreatitis.	IIa	B

2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias
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CLINICAL PRACTICE GUIDELINE

2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association

4.2.9. Management of Hypertriglyceridemia

Recommendations for Management of Hypertriglyceridemia
Referenced studies that support recommendations are summarized in the Evidence Table.

COR	LOE	RECOMMENDATIONS
1	B-NR	1. In adults with persistently elevated TG levels ≥150 mg/dL (1.7 mmol/L), after evaluation and management of secondary causes,[1] lifestyle management (consuming a diet that consists of low added sugars, as well as reduced alcohol and saturated fat intake, routine exercise, and weight loss of 5%-10% of body weight if overweight or obese) is recommended as a first-line approach to reduce TG levels (Figure 2).[2,3]
1	B-R	2. In adults with clinical ASCVD and LDL-C ≥55 mg/dL (1.4 mmol/L) and non-HDL-C ≥85 mg/dL on maximally tolerated statin with persistently elevated TG levels ≥150 to 999 mg/dL (1.7-11.3 mmol/L), intensification of LDL-C-lowering therapy is recommended to reduce ASCVD risk.[4-6]
1	B-R	3. In adults with FCS and fasting TG ≥1000 mg/dL (11.3 mmol/L), olezarsen is recommended as an adjunct to diet to lower TG levels and reduce the risk of pancreatitis.[7,8]
2b	B-R	4. In adults ≥50 years of age with clinical ASCVD or with diabetes and ≥1 ASCVD risk factors, with persistently elevated TG levels ≥150 to 499 mg/dL (1.7-5.6 mmol/L), and LDL-C <100 mg/dL (2.6 mmol/L) on maximally tolerated statin, the addition of IPE may be reasonable to lower ASCVD risk. (See Figure 9 in Section 4.2.5, "Diabetes in Adults Without Established ASCVD.")[9,10]

EPA Interferes with CVD Continuum at Multiple Points to Reduce Events

	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Plaque Progression			
EPA Increases	Endothelial function Nitric oxide bioavailability Membrane lipid stability Vasodilation Free radical scavenging	EPA/AA ratio IL-10 Bioactive lipid metabolites SPMs	Fibrous cap thickness Lumen diameter Plaque stability Regression of low attenuation plaque
EPA Decreases	Cholesterol crystalline domains Ox-LDL RLP-C ICAM-1 Adhesion of monocytes Arterial stiffness	Macrophage foam cells IL-6 hsCRP Lp-PLA_2 MMPs ApoC-III	Plaque volume (low attenuation, fibrofatty, non-calcified) Thrombosis Platelet activation

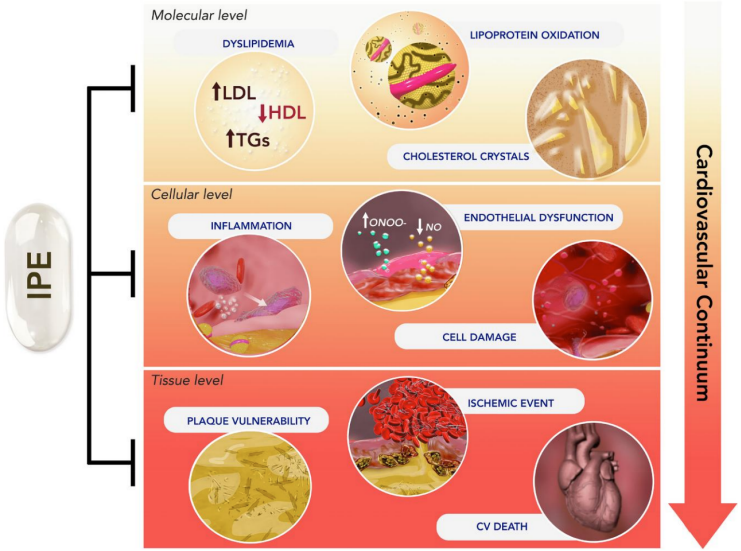

Figure 5 EPA interrupts the cardiovascular disease continuum at multiple points. There are multiple mechanisms associated with the cardiovascular disease continuum, starting with endothelial dysfunction and dyslipidaemia and culminating in ischaemic events, organ damage and death. Clinical trials, most notably REDUCE-IT, showed treatment with icosapent ethyl (IPE) reduced risk of major adverse cardiovascular events by 25%. The active ingredient of IPE, EPA, has shown beneficial activity at several points along the continuum, all of which contribute to the overall risk reduction.