DAL DIABETOLOGO AL CARDIOLOGO: L'ORIZZONTE È PIÙ LONTANO

MODERATORI: Alessandra Clerico, Maria Chantal Ponziani

News 4.

Il rischio cardiovascolare residuo. Aggiornamenti terapeutici: l'Icosapentil Etile

Francesco Tassone, MD, PhD,

S.C. Diabetologia Territoriale ASL TO5

A.S.L. TO5

Azienda Sanitaria Locale
di Chieri, Carmagnola, Moncalieri e Nichelino

Il dr. FRANCESCO TASSONE dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche seguenti:

DAICHI SANKYO, ASTA ZENECA, LILLY, NOVO, BOEHRINGHER, GUIDOTTI,

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

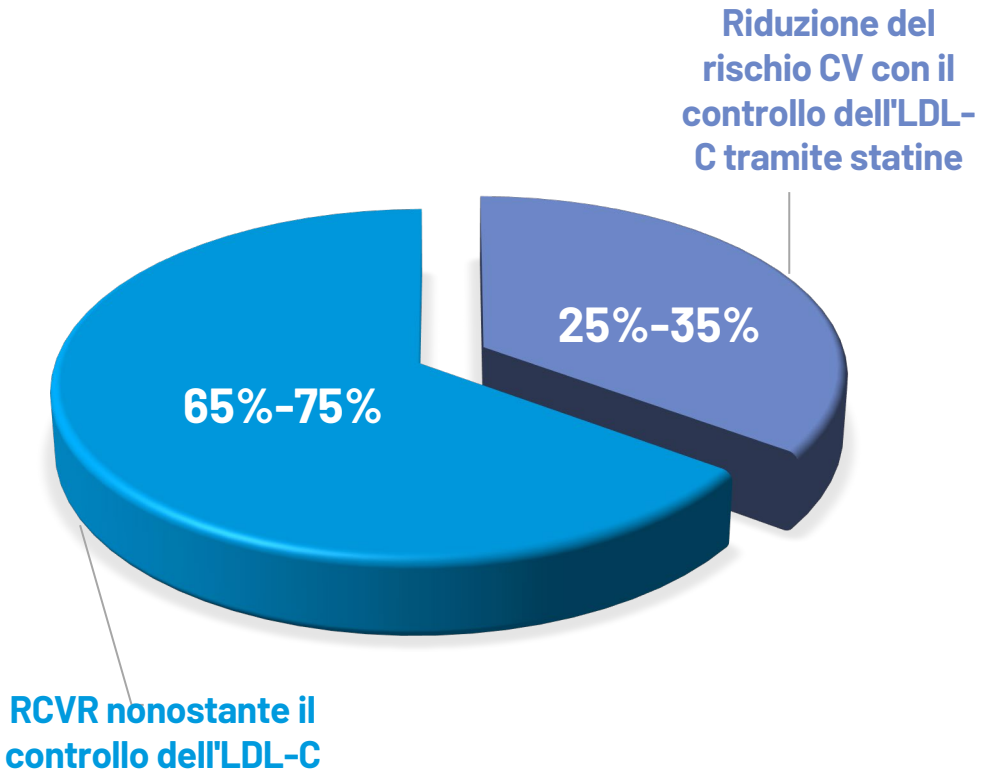
Rischio Cardiovascolare Residuo (RCVR)

Il «Rischio cardiovascolare residuo», è definito come un qualsiasi fattore di rischio causale per l'ASCVD, non controllato in modo ottimale. Esistono una miriade di fattori che determinano il rischio residuo, inclusi quelli non direttamente affrontati dalle **attuali strategie di gestione del rischio stesso**.

Dhindsa DS., et al., 2020

Il RCVR permane con lo standard di cura

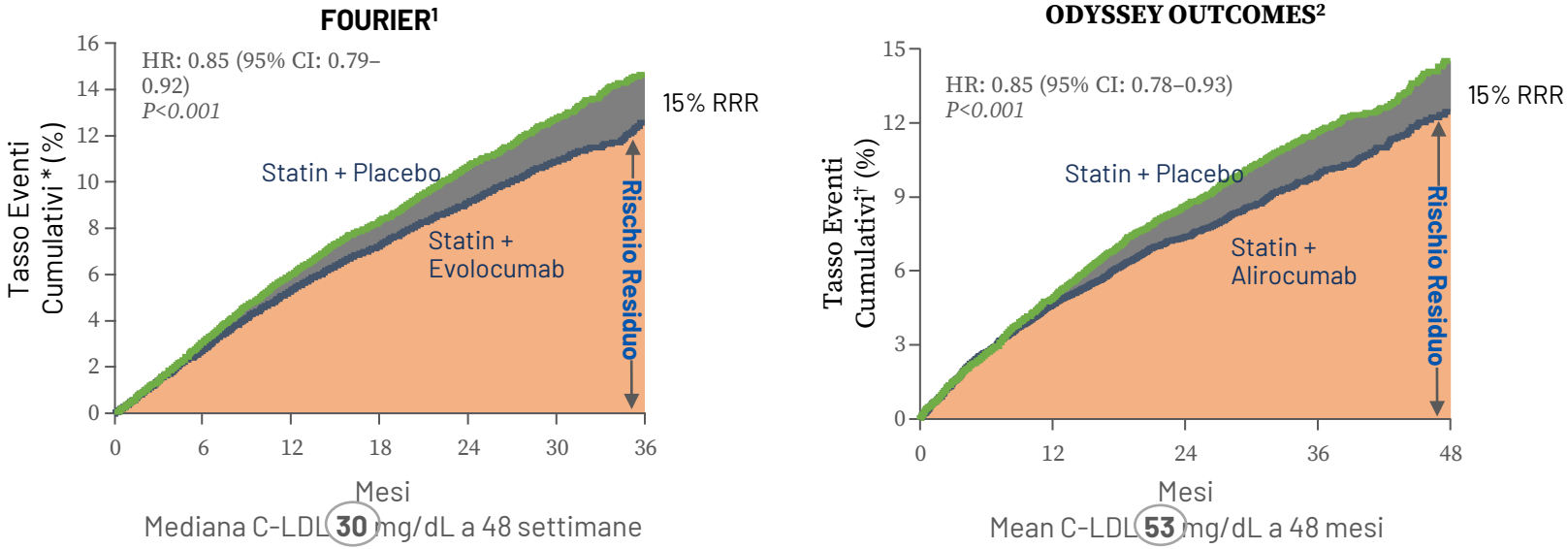
Proporzione di eventi Cardiovascolari che si verificano nei soggetti trattati, secondo le Linee Guida, con statine e/o farmaci ipocolesterolemizzanti.



CV, cardiovascolare; CVR, rischio cardiovascolare; LDL-C, lipoproteine-colesterolo a bassa densità.

60. Hong KN, et al., 2017; 61. Collins R, et al., 2016; 62. Boekholdt SM, et al., 2014; 63. Ganda OP, et al., 2018.

Il Rischio Residuo persiste nonostante l'aggressiva riduzione del C-LDL con gli inibitori della PCSK9



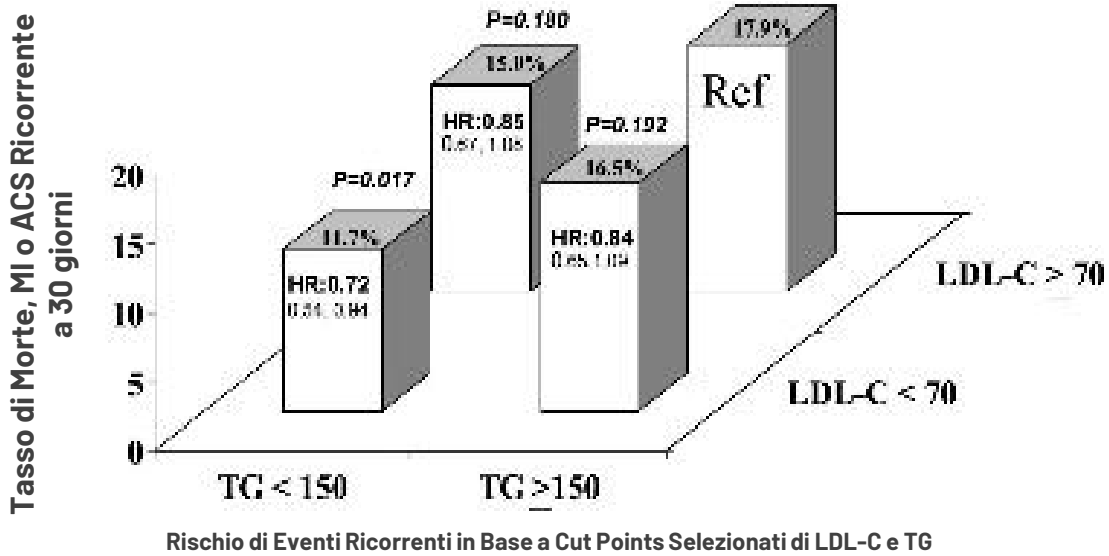
**Composite of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation[1]; †Composite of death due to coronary heart disease, non-fatal MI, fatal or non-fatal ischaemic stroke or hospitalisation for unstable angina.[2]*

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.

1. Sabatine MS et al NEJM 2017, DOI: 10.1056/NEJMoa1615664
2. Schwartz GG et al NEJM 2018, DOI: 10.1056/NEJMoa1801174

I Trigliceridi a digiuno predicono eventi ischemici ricorrenti in pazienti con Sindrome Coronarica Acuta o ASCVD trattati con Statine ad alto dosaggio

Tasso di eventi e rischio aggiustato di morte, infarto miocardico (IM) e sindrome coronarica acuta (ACS) ricorrente tra i 30 giorni e i 2 anni di follow-up con LDL-C e TG raggiunti in base ai cut-point designati di 70mg/dl e 150mg/dl, rispettivamente



Rischio di Eventi Ricorrenti in Base a Cut Points Selezionati di LDL-C e TG

Prove-it

From Miller M, et al., 2008

65. Miller M, et al., 2008; 66. Schwartz GG, et al., 2015.

Risk for all-cause mortality and ASCVD events in 158,042 low-to-moderate risk Italian individuals according to TG levels: TG-REAL Study

Triglycerides levels	Events (number)	Crude incidence (1000 person/year)	Age and gender adjusted HR	Multivariate adjusted* HR
ASCVD events				
Normal TG	2,076	6.4	1	1
High TG (≥150-500 mg/dl)	459	14.8	2.21 [1.99-2.44, p<0.001]	**1.61** [1.43-1.82, p<0.001]
Very High TG (>500 mg/dl)	6	16.2	3.85 [1.72-8.58, p=0.001]	**2.30** [1.02-5.18, p<0.05]
Total	2,541	7.2		
Overall mortality				
Normal TG	5,346	16.4	1	1
High TG (≥150-500 mg/dl)	747	24.2	1.61 [1.49-1.74, p<0.001]	**1.49** [1.36-1.63, p<0.001]

Arca M et al. JAHA 2020;9:e015801

Terapie ipolipemizzanti di vecchia generazione: nessuna evidenza di benefici CV

Agenti Riduttori dei TG	Studi Chiave*	Riscontro 1° endpoint MACE?
Fibrati	ACCORD[1] FIELD[2] PROMINENT[11]	✕
Niacina	AIM-HIGH[3] HPS2-THRIVE[4]	✕
Prescrizione e integratori, miscele EPA + DHA	RISK & PREVENTION,[5] ORIGIN,[6] OMEGA,[7] ASCEND,[8] VITAL,[9] STRENGTH[10]	✕

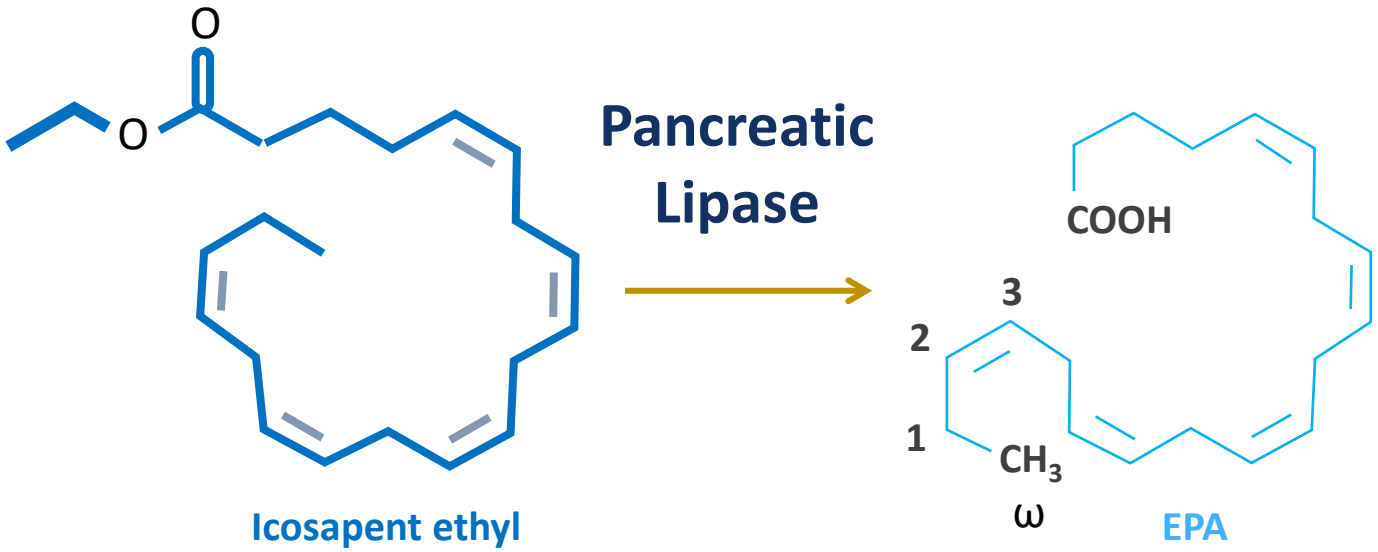
*ACCORD: Action to Control Cardiovascular Risk in Diabetes; ASCEND: A Study of Cardiovascular Events in Diabetes; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; OMEGA: Effect of Omega-3 Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; ORIGIN: Outcome Reduction with an Initial Glargine Intervention; STRENGTH: Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia;
VITAL: Vitamin D and Omega-3 Trial.

CV, cardiovascolare; DHA, acido docosaesaenoico; EPA, acido eicosapentaenoico; MACE, evento cardiovascolare avverso maggiore; TG, trigliceridi.

68. ACCORD Study Group. 2010; 69. FIELD Study Investigators. 2005; *70. Risk and Prevention Study Collaborative Group. 2013; 71. ORIGIN Trial Investigators. 2012; 72. OMEGA Study Group. 2010; 73. ASCEND Study Collaborative Group. 2018; 74. Manson JE, et al., 2019; 75. Nicholls SJ et al., 2020;* *11 https://www.prnewswire.com/news-releases/kowa-to-discontinue-k-877-pemafibrate-prominent-cardiovascular-outcomes-study-301520956.html*

Icosapent Ethyl

Chemical Structure



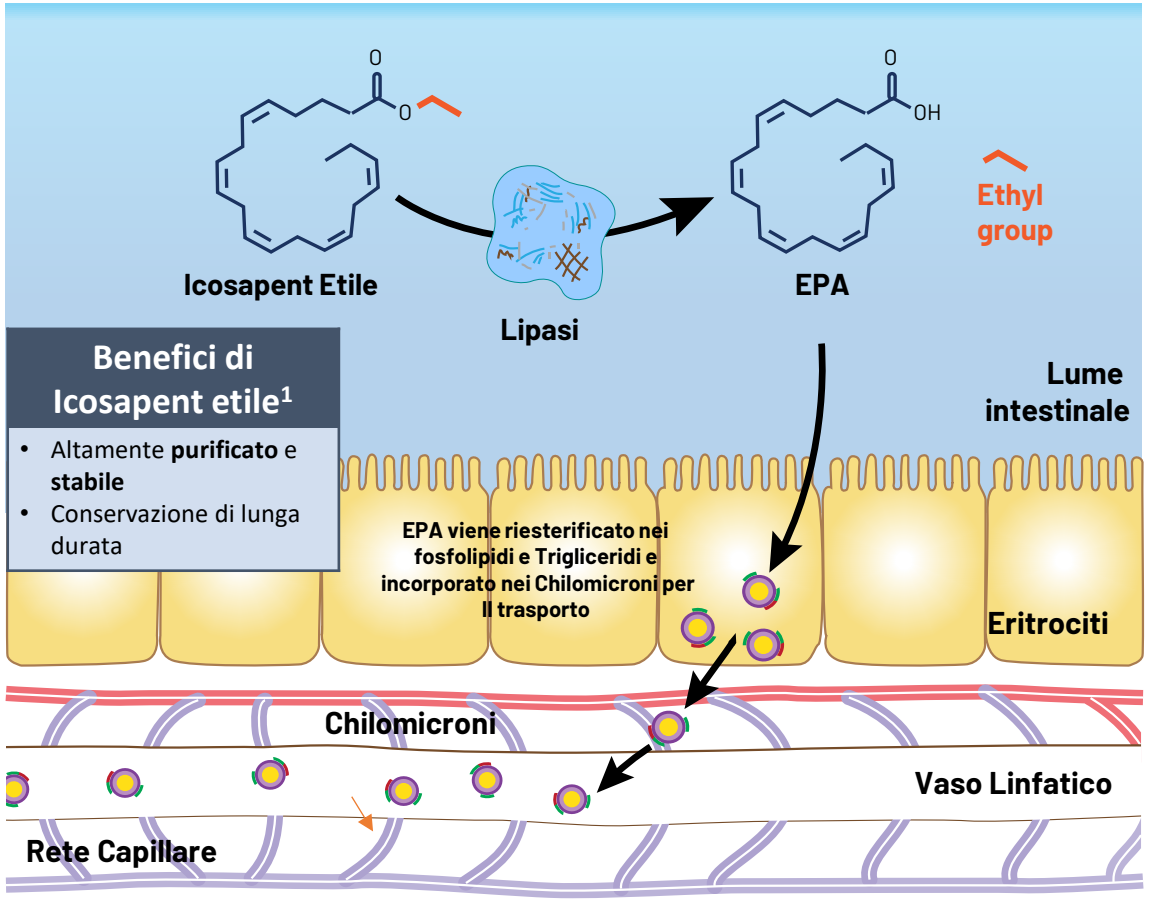
$C_{22}H_{34}O_2$ **Mol. Wt. 330.41**

- Icosapent ethyl is a stable ethyl ester of the omega-3 fatty acid EPA.[1]
- It is a 20-carbon fatty acid, with 5 double bonds, the first double bond being the third carbon atom (20:5, n-3 [Omega 3; ω-3]).[1]
- It is a prodrug, its molecular structure allows for effective delivery of the active ingredient EPA.[1]
- Upon icosapent ethyl de-esterification via the action of pancreatic lipase (ethyl ester cleavage), EPA is efficiently absorbed through the small intestine to enter the circulation.[1,2]

EPA, eicosapentaenoic acid.

1. VASCEPA [package insert]. Bridgewater, NJ: Amarin Pharma, Inc; 2019. **2.** Vazkepa [Summary of Product Characteristics]. Dublin, Ireland: Amarin Pharmaceuticals Ireland Limited; 2021.

IPE: Metabolismo



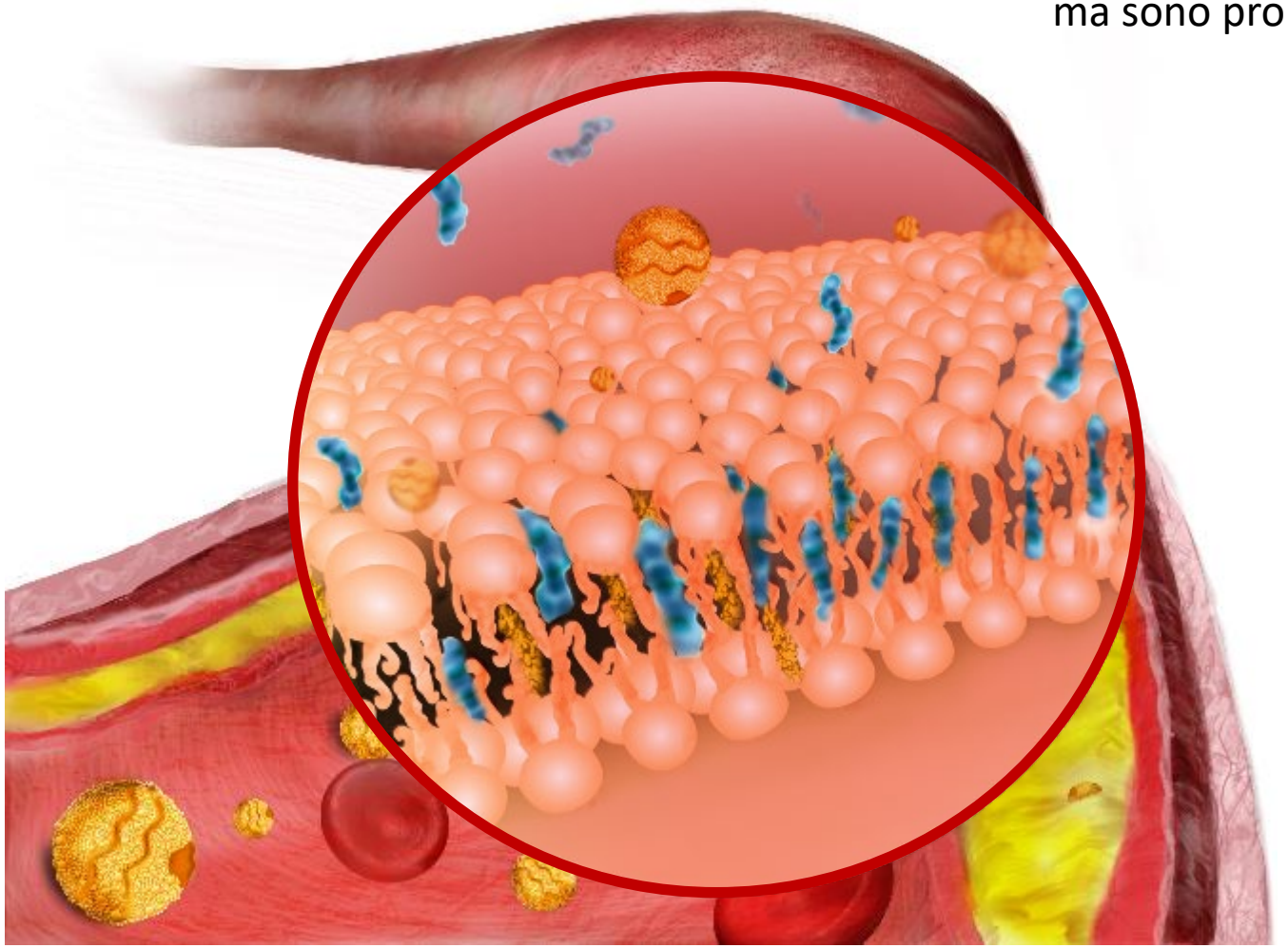
- L'aggiunta del Gruppo etil estere consente:[2]
  - Maggiore purificazione
  - Elevata concentrazione
  - Elevata stabilità
  - Lunga durata di conservazione
- Icosapent etile viene de-esterificato in EPA nell'intestino tenue e assorbito.[2]
- Una volta assorbito, EPA è trasportato nel sangue all'interno dei chilomicroni.[2]
- Dopo circa 5 ore EPA raggiunge il picco di concentrazione nel plasma.[2]
- 99% di EPA è legato alle proteine plasmatiche.[2]
- Eliminazione plasmatica $t_{1/2}$ = 89 ore.[2]
- L'eliminazione avviene tramite metabolismo epatico.[2]
- Non subisce l' escrezione renale.[2]

EPA, eicosapentaenoic acid; $t_{1/2}$, half-life.

1. Wang X, et al. *Curr Diab Rep*. 2020;20(11):65; **2.** Brinton EA, et al. *Lipids Health Dis*. 2017;16(1):23.

EPA ha effetti benefici su più processi aterosclerotici

- I meccanismi d'azione che contribuiscono alla riduzione degli eventi cardiovascolari con IPE non sono completamente compresi, ma sono probabilmente multifattoriali.



Miglioramento della funzione endoteliale

- ↑ Produzione di NO (ossido nitrico)
- ↑ Vasodilatazione endotelio-dipentende
- ↓ Specie reattive dell'ossigeno

Effetti Anti-infiammatori

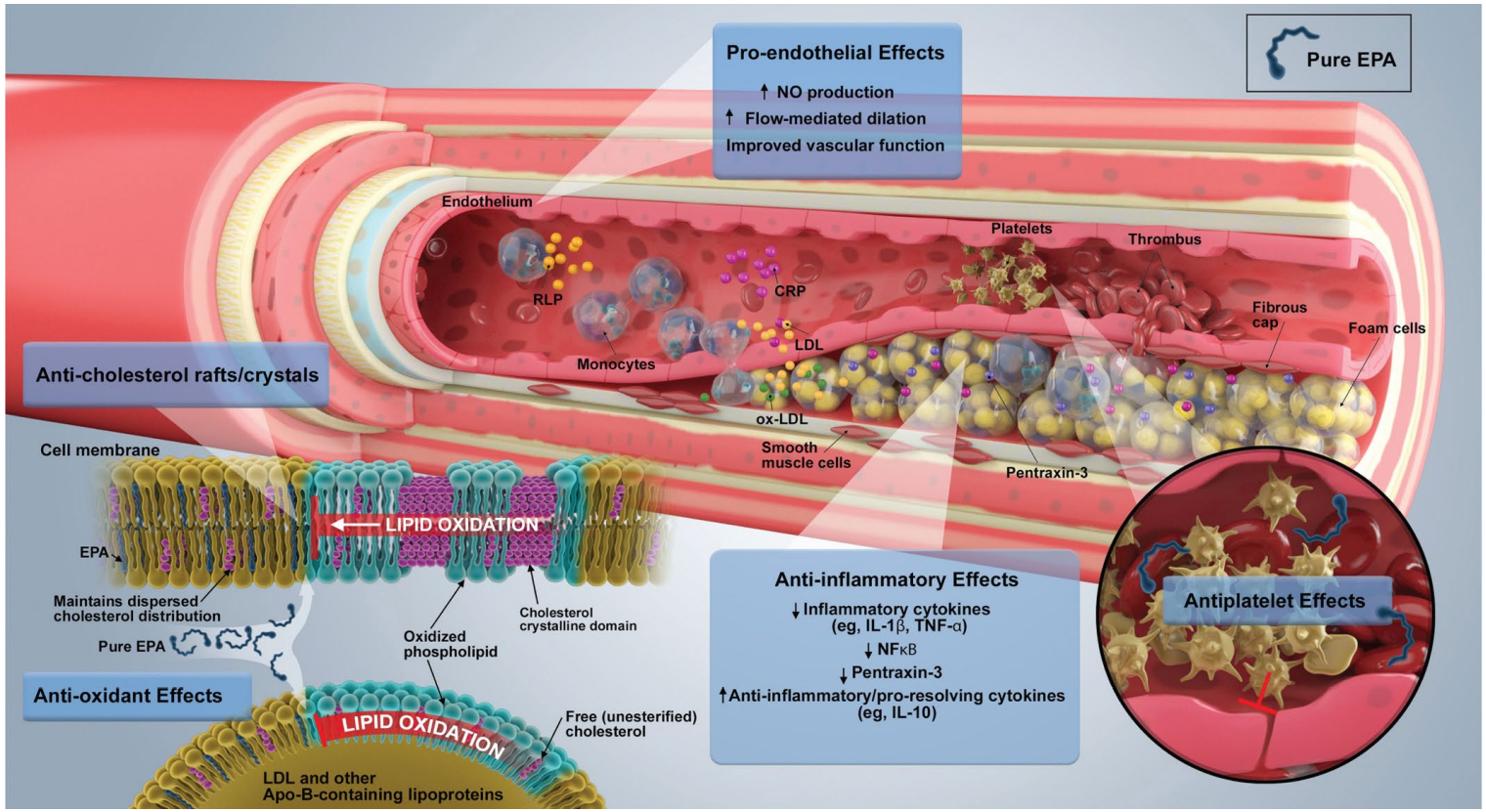
- ↓ Eicosanoidi e citochine pro-infiammatorie
- ↓ Reclutamento di cellule infiammatorie

Stabilizzazione della Placca

- ↓ Formazione, progression e rottura della placca
- ↓ Trombosi
- ↓ Attivazione delle piastrine
- ↑ Spessore del cappuccino fibroso

1. Mason RP. *Curr Atheroscler Rep*. 2019;21(1):2; 2. Ganda OP et al. *J Am Coll Cardiol*. 2018;72(3):330-343; 3. Borow KM et al. *Atherosclerosis*. 2015;242(1):357-366.

EPA: Effetto sulla progressione della placca



EPA AUMENTA

- Spessore del cappuccio fibroso
- Diametro del lume
- Stabilità della placca

EPA RIDUCE

- Il volume della placca
- La rigidità arteriosa
- La vulnerabilità della placca
- La trombosi
- L'attivazione piastrinica

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*;

Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial

reduce-it

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*

REDUCE-IT ha valutato pazienti in trattamento con statine, con LDLc ben controllato e molteplici fattori di rischio CV

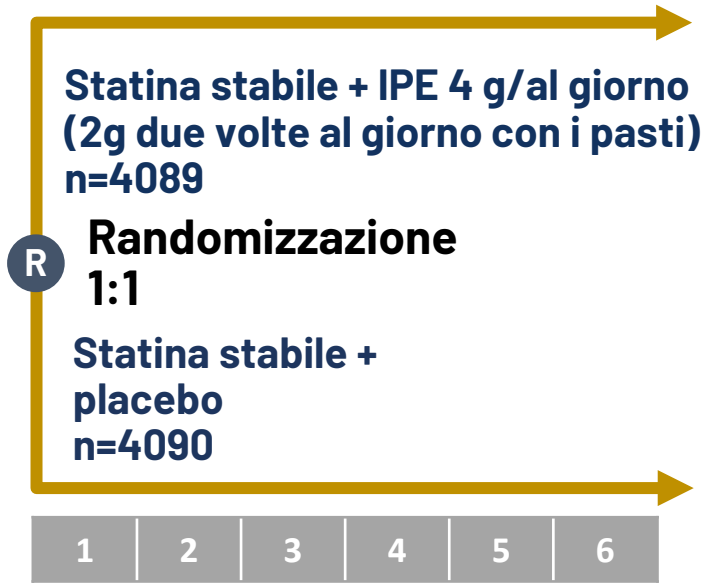
PATIENTS	AT RISK FOR	RANDOMISATION
8179 Pazienti… ▪ Uomini e Donne di età ≥45 anni in terapia stabile con statina +/- ezetimibe ▪ LDL-C 40 – 100 mg/dl ; mediana al basale di 74 mg/dl	**At High Risk for CV Events due to:** **Livelli di TG da lievi a moderati** ▪ TG 135 –500 mg/dl; mediana al basale 216 mg/dl **- E -** ▪ CVD accertata (prevenzione secondaria) **- O -** ▪ Diabetes mellito + età ≥50 anni + almeno un fattore di rischio per CVD (prevenzione primaria)	**Randomisation 1:1** **Trattamento** ▪ Statina stabile + IPE 4 g/giorno (2 g 2 volte al giorno con i pasti) **- O -** ▪ Statina stabile + placebo

CV: cardiovascular; CVD: cardiovascular disease; IPE: icosapent ethyl; LDL-C: low density lipoprotein-cholesterol; REDUCE-IT: Reduction of CV Events with Icosapent Ethyl-Intervention Trial; TG: triglycerides.

1. Bhatt DL, et al. *Clin Cardiol*. 2017;40(3). **2**. Bhatt DL, et al. *N Engl J Med*. 2019;380(1).

REDUCE-IT: Trial multi centrico, randomizzato, doppio cieco, controllato con placebo, event-driven

- 473 centri
- 11 paesi



Mediana di follow-up: 4.9 anni

Primary Endpoint

Time to first 5-point composite MACE:

- Morte CV
- IM non fatale
- Ictus non fatale
- Rivascolarizzazione coronarica
- Ospedalizzazione per agina instabile

Key Secondary Endpoint

Time to first 3-point composite MACE:

- Morte CV
- IM non fatale
- Ictus non fatale

IPE: icosapent ethyl

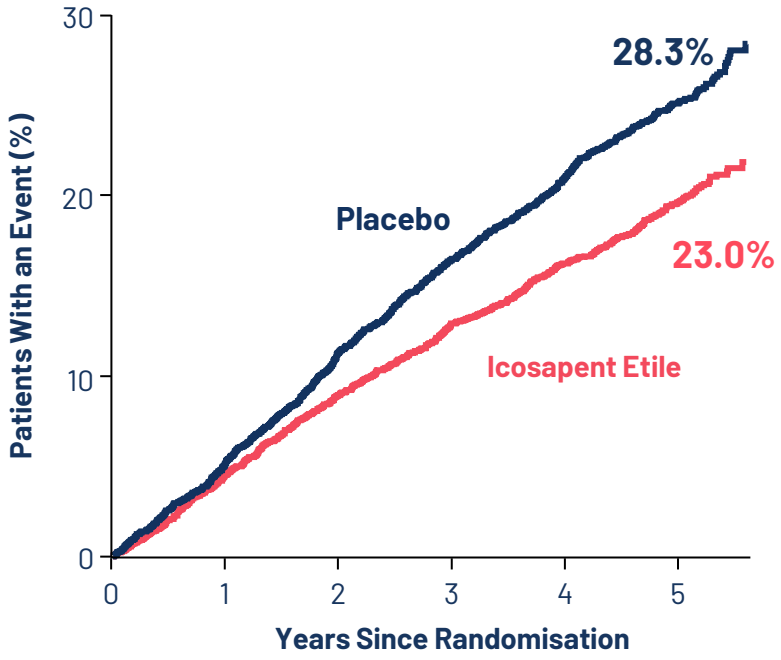
1. Bhatt DL et al. *Clin Cardiol*. 2017;40(3); **2**. Bhatt DL et al. *N Engl J Med*. 2019;380(1).

Le caratteristiche al basale erano simili tra i gruppi in trattamento[1-2]

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	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 Endpoint:
Morte CV, IM, Ictus, Rivascolarizzazione Coronarica, Angina Instabile



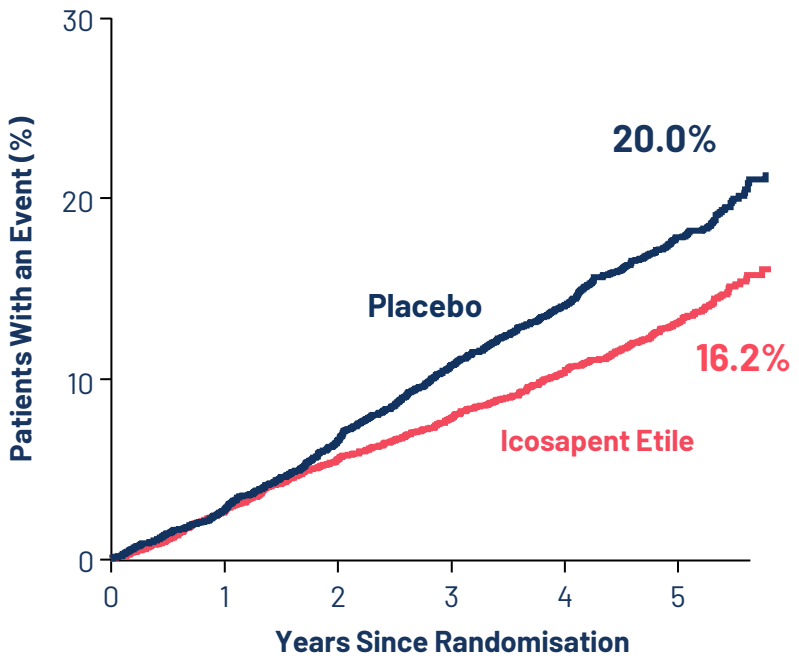
L'End-point primario si è verificato nel 17.2% dei pazienti nel gruppo Icosapent etile rispetto al 22.0% del gruppo placebo, con una differenza assoluta del 4.8%[1] tra i gruppi.

Hazard Ratio = 0.75
(95% CI: 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI: 15–33)
***P*=0.00000001**

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

1. Bhatt DL, et al. *N Engl J Med* 2019;380:11-22.
2. Bhatt DL, et al. Presented at AHA 2018, Chicago.

Key Secondary Endpoint: Morte CV, IM, Ictus



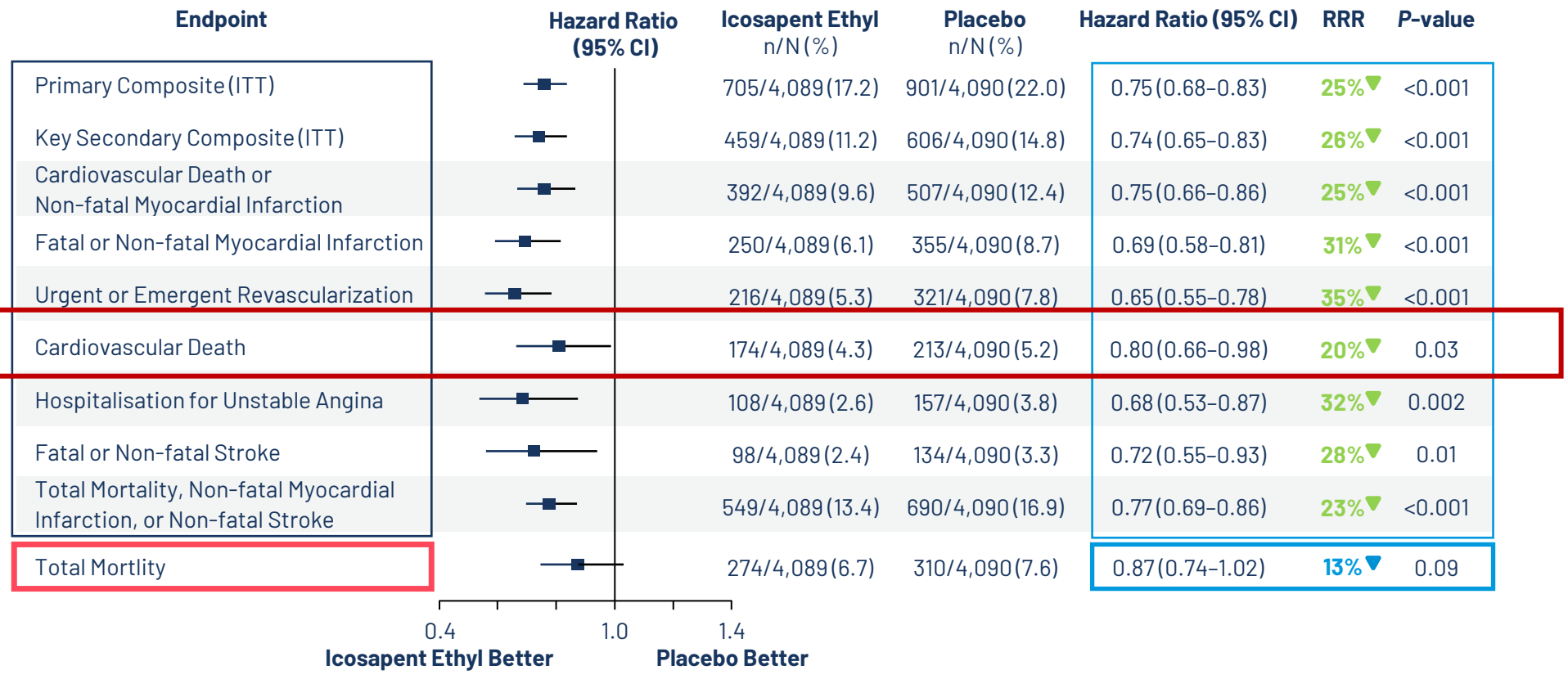
L'End-point secondario si è verificato nel 11.2% dei pazienti del gruppo Icosapent etile rispetto al 14.8% del gruppo placebo, con una differenza assoluta del 3.6% tra i gruppi.

Hazard Ratio = 0.74
(95% CI: 0.68–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI: 20–47)
***P*=0.00000006**

ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NNT, number needed to treat; RRR, relative risk reduction.

1. Bhatt DL, et al. *N Engl J Med* 2019;380:11-22.
2. Bhatt DL, et al. Presented at AHA 2018, Chicago.

Test Gerarchico Prespecificato[1,2]

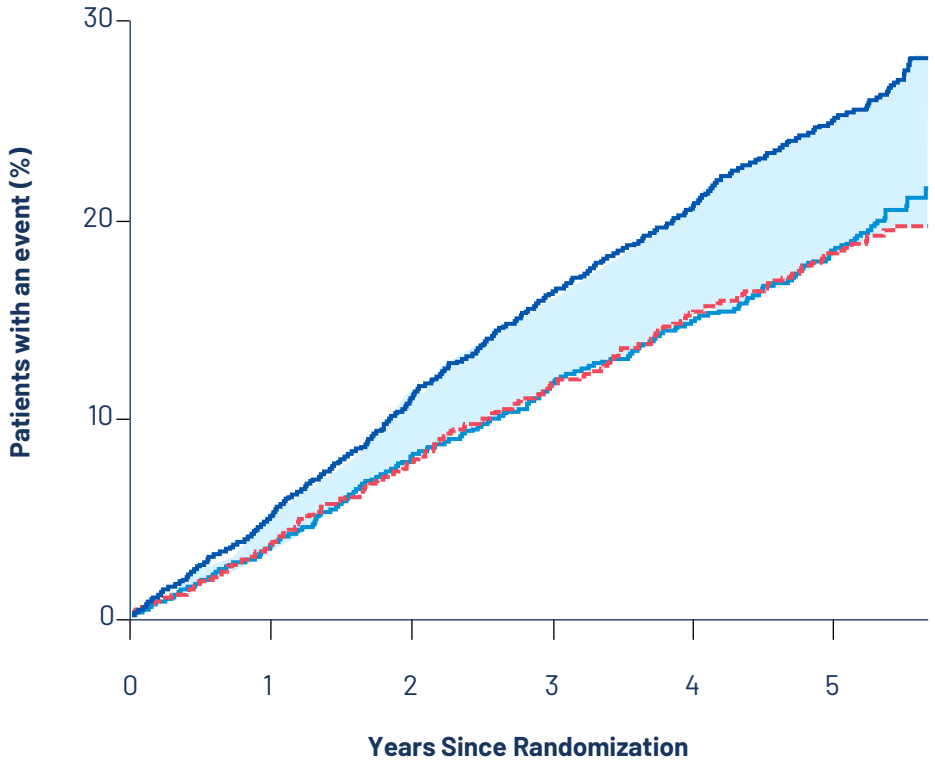


CI, confidence interval; ITT, intent-to-treat; RRR, relative risk reduction..

1. Bhatt DL, et al. *N Engl J Med* 2019;380:11-22.
2. Bhatt DL, et al. Presented at AHA 2018, Chicago.

Rischio CV: Riduzione considerevole indipendente dai livelli di TG raggiunti e minimamente influenzata dalle variazioni dei biomarcatori

Primary endpoint stratified by achieved TG level (above or below 150 mg/dL) at 1 year



IPE, icosapent ethyl.

1. Bhatt DL et al; for REDUCE-IT Investigators. *N Engl J Med*. 2019;380:48(1):Supplemental Appendix, p48.

Il beneficio CV di IPE

- Non è determinato dal raggiungimento di livelli "normali" di TG inferiori a 1.7 mmol/L (150 mg/dL)
- sembra essere sostanzialmente guidato da effetti multifattoriali che vanno oltre le variazioni dei biomarcatori
- Offre l'opportunità di trattare il rischio dei pazienti piuttosto che un dato di laboratorio

Statina + Placebo

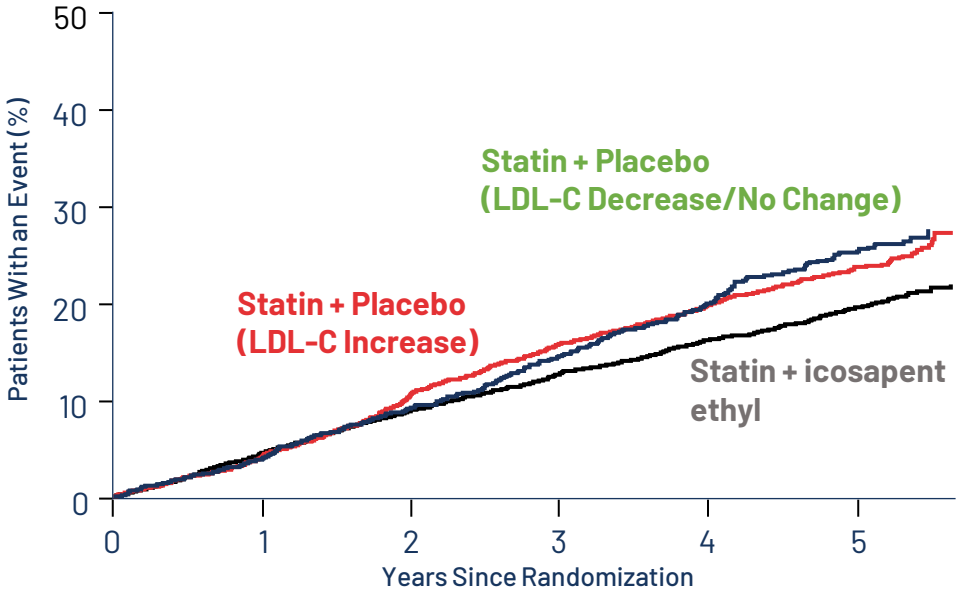
IPE TG ≥1.7 mmol/L (150 mg/dL)
HR (95% CI) = 0.71 (0.63–0.79)

IPE TG <1.7 mmol/L (150 mg/dL)
HR (95% CI) = 0.71 (0.60–0.81)

Risultati simili sono stati osservati per l'end-point secondario

CV Risk: Robust Reduction Independent of LDL-C Levels

Primary Endpoint by LDL-C Level at 1 Year

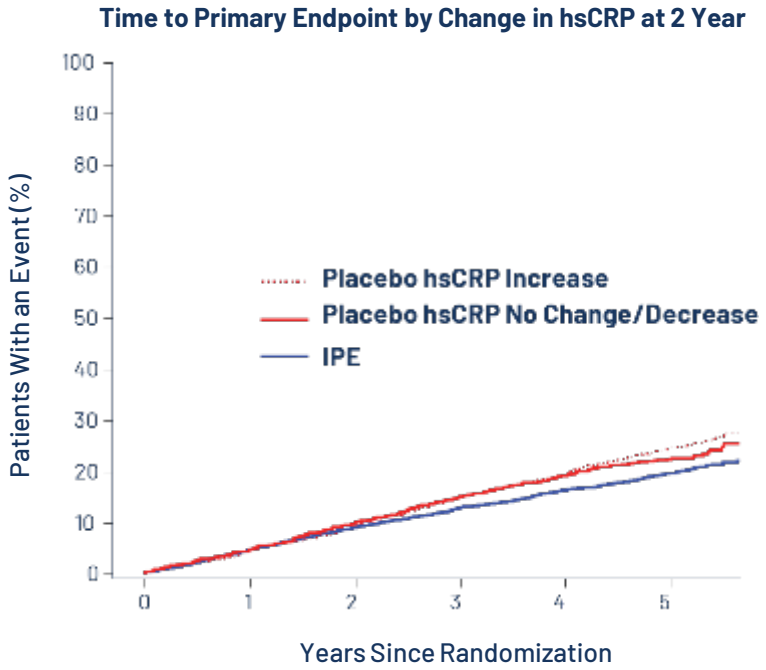


Compared to icosapent ethyl, there was no difference in outcomes for placebo patients with increased versus decreased LDL-C at 1 year follow-up

Subgroup Comparisons	HR (95% CI)
icosapent ethyl vs Placebo (LDL-C Increase)	0.79 (0.70–0.88)
icosapent ethyl vs Placebo (LDL-C Decrease/No Change)	0.79 (0.69–0.91)
Placebo (LDL-C Increase) vs Placebo (LDL-C Decrease/No Change)	1.01 (0.87–1.17)

Bhatt DL ,et al. N Engl J Med. 2019; 380:11-22.

CV Risk: Robust Reduction Independent of hs-CRP Levels

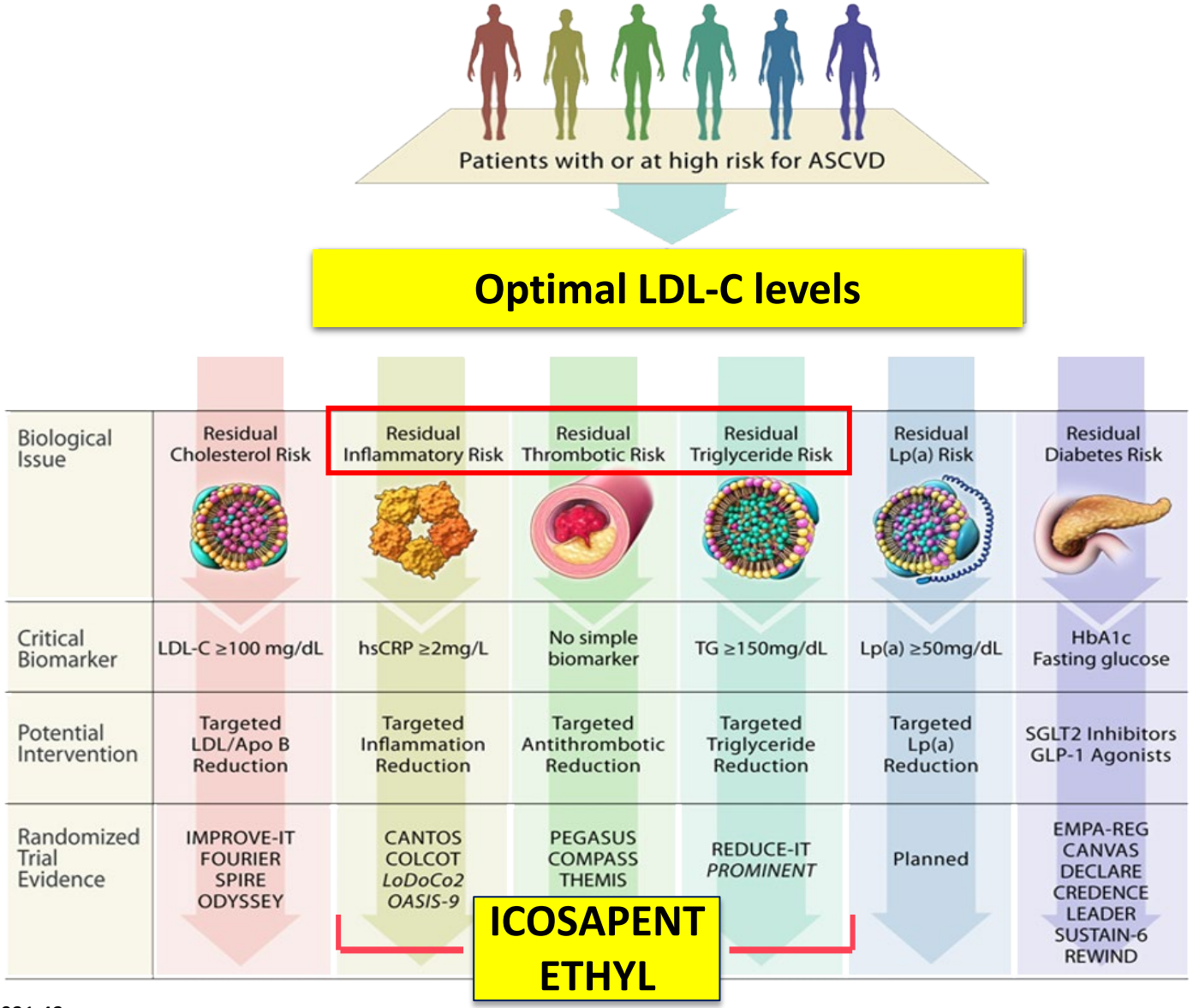


Compared to icosapent ethyl, there was no difference in outcomes for placebo patients with increased versus decreased hs-CRP at 2 years follow-up

Subgroup Comparisons	HR (95% CI)
icosapent ethyl vs Placebo (hs-CRP Increase)	0.79 (0.71–0.89)
icosapent ethyl vs Placebo (hs-CRP Decrease/No Change)	0.83 (0.72–0.96)
Placebo (hs-CRP Increase) vs Placebo (hs-CRP Decrease/No Change)	1.05 (0.90–1.22)

Olshansky, et al; Eur Heart J. 2020; 22 (Supplement J), J34–J48;

Icosapent ethyl addresses the TG component of residual risk

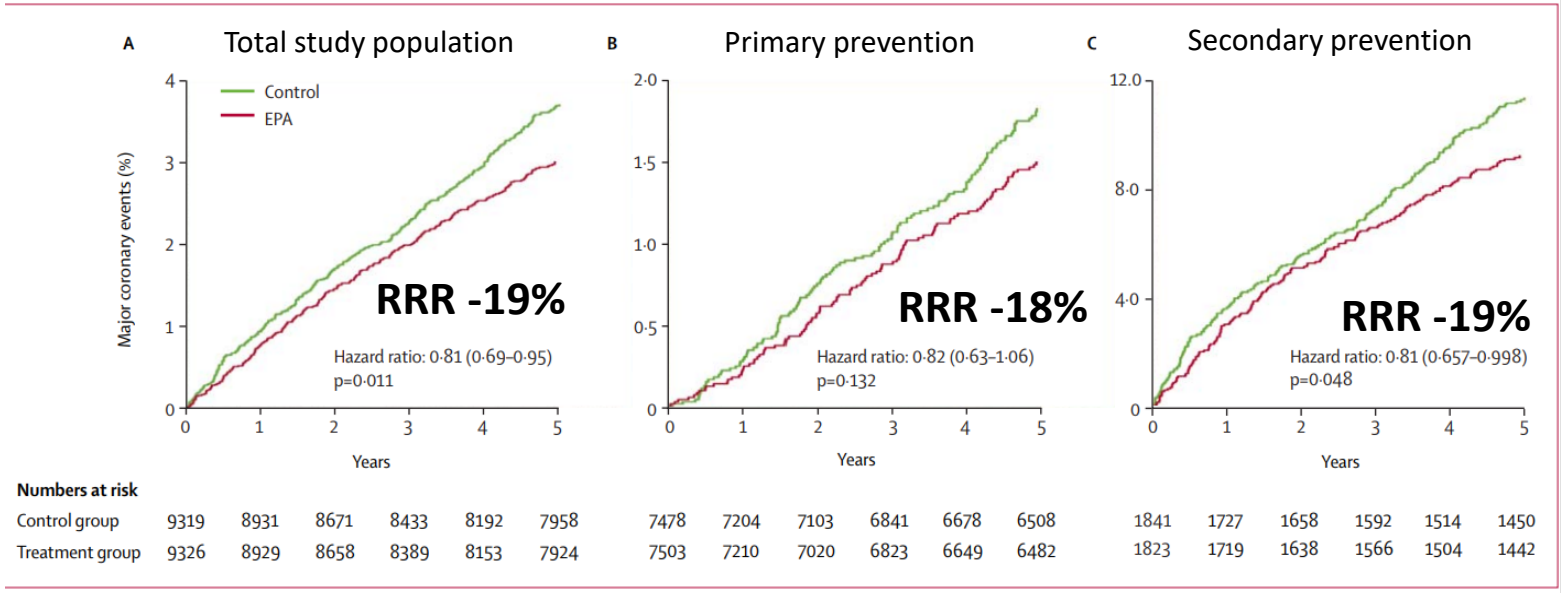


Lawler et al. Eur Heart J 2021;42

JELIS: FIRST STUDY TO REPORT CV BENEFITS OF 1.8 g EPA IN JAPANESE POPULATION

Some important features:

- **18645 patients**
- **Open label trial**
- **5-year follow-up**
- **Not placebo controlled** (usual care with statins in both arms)
- Average **TG levels: 153 mg/dL**
- **Japanese population** (lower CV risk, **higher baseline EPA levels**)
- 69% women
- Relatively **low statin doses**



Kaplan-Meier estimates of incidence of coronary events in the total study population (panel A), the primary prevention arm (panel B) and the secondary prevention arm (panel C)

The 5-year cumulative rate of major coronary events was 2.8% in the EPA group and 3.5% in controls, resulting in **a significant relative risk reduction of 19% in the EPA group (*P*=0.011).**

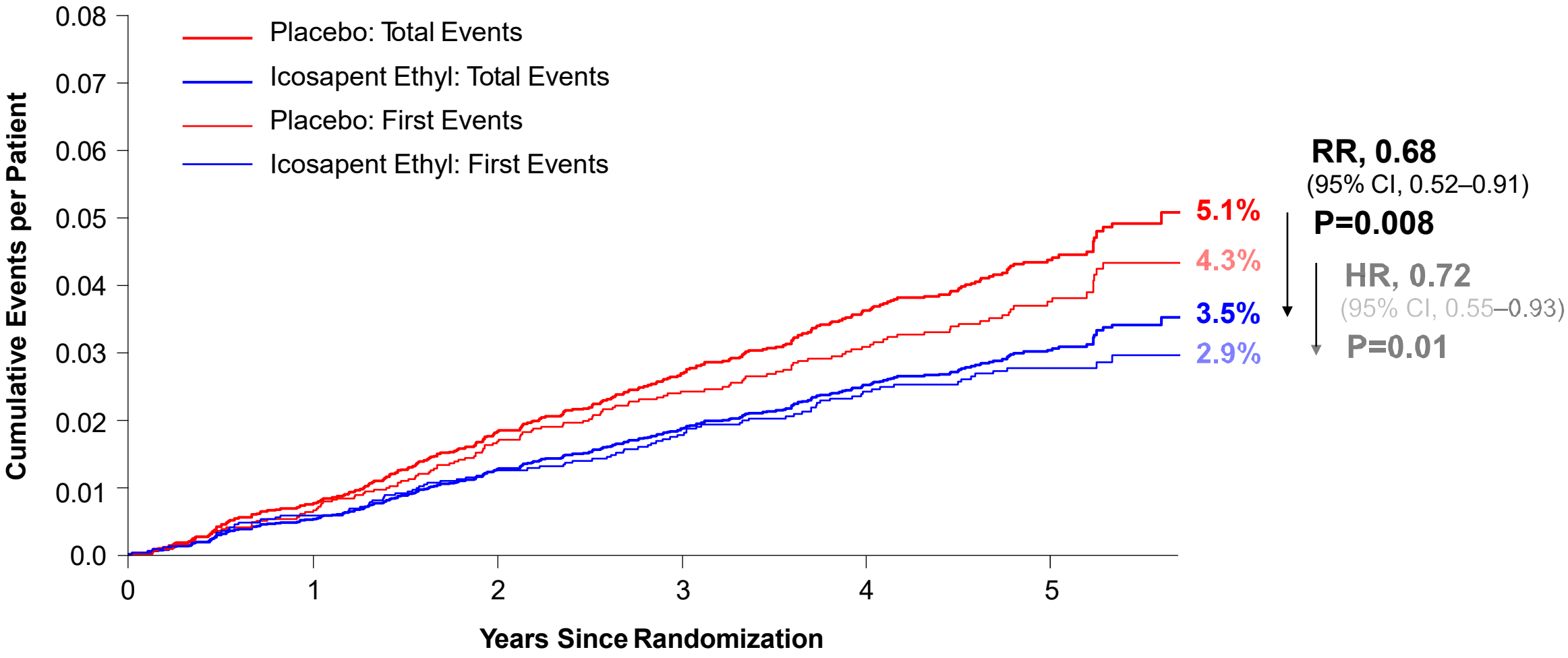
Major coronary events were reduced by 19% (secondary prevention subgroup: 158 [8.7%] in the EPA group vs 197 [10.7%] in the control group; P=0·048).

Yokoyama M, et al. *Lancet*. 2007;369(9567).

REDUCE-IT SOTTOANALISI

Icosapent Ethyl Reduced First and Total Strokes

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

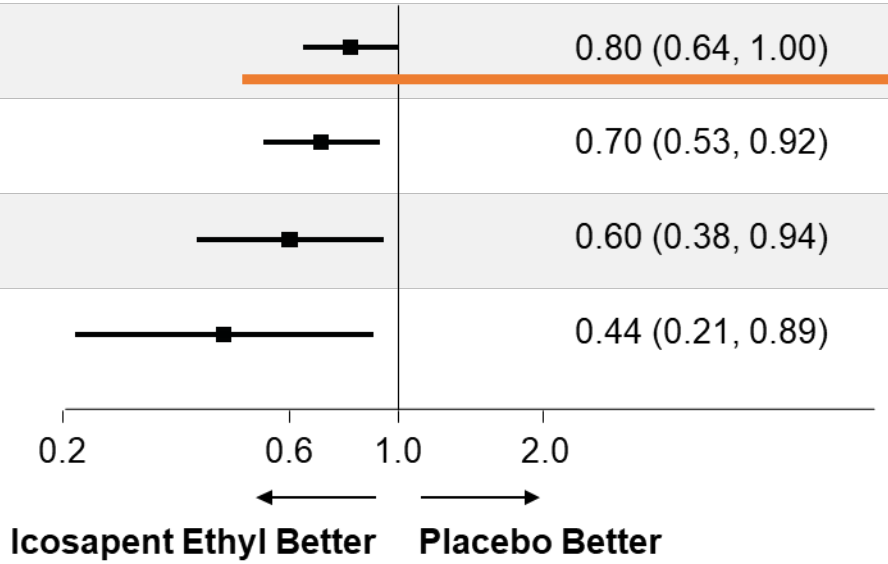


Bhatt DL. ISC 2021, virtual.

TOTAL MORTALITY, CARDIOVASCULAR DEATH, CARDIAC ARREST AND SUDDEN CARDIAC DEATH IN PATIENTS WITH PRIOR MI

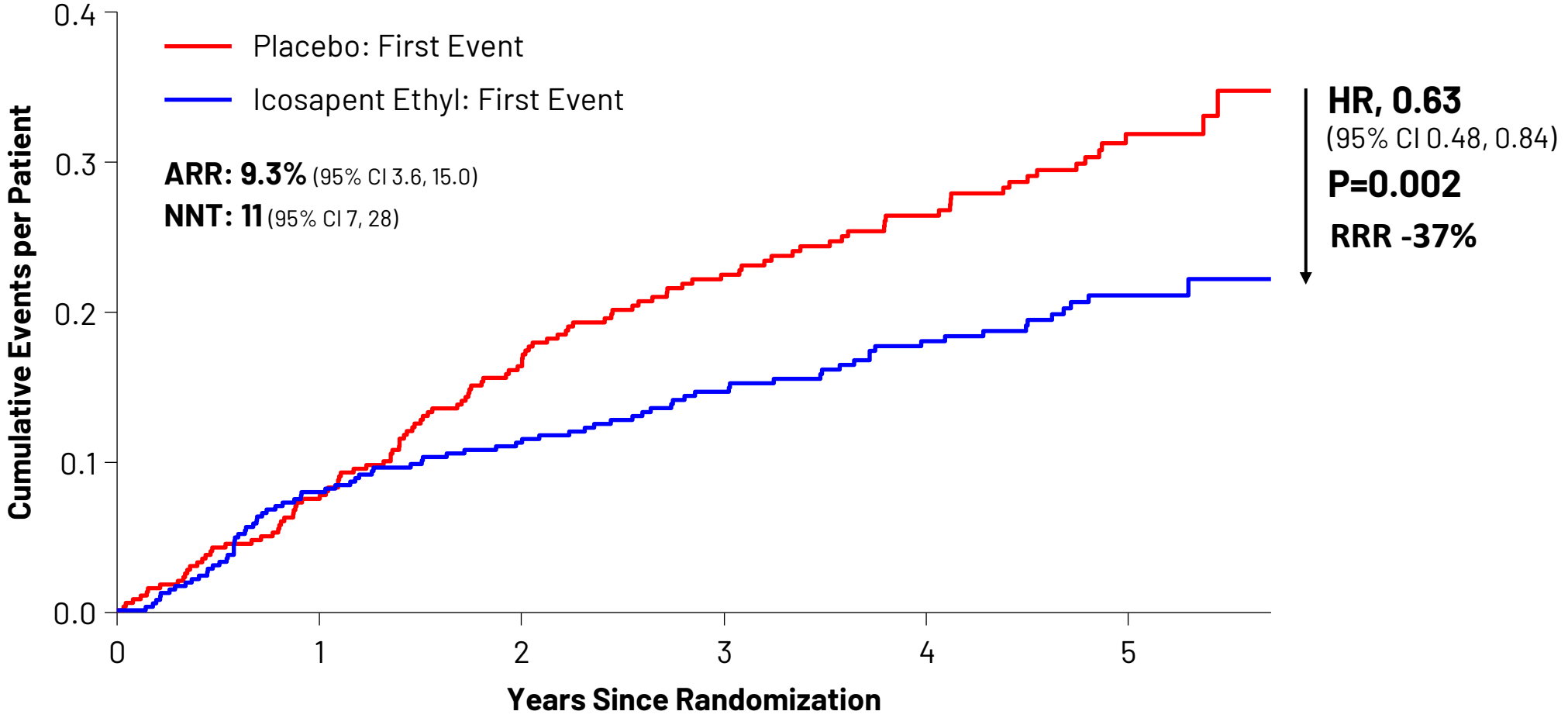
reduce-it PRIOR MI

Endpoint	Icosapent Ethyl	Placebo	Icosapent Ethyl vs. Placebo	P-value	
	n/N (%)	*n/N (%)*	*HR (95% CI)*		
Total Mortality	136/1870 (7.3)	163/1823 (8.9)	0.80 (0.64, 1.00)	0.054	**-20%**
Cardiovascular Death	84/1870 (4.5)	116/1823 (6.4)	0.70 (0.53, 0.92)	0.01	**-30%**
Sudden Cardiac Death	31/1870 (1.7)	50/1823 (2.7)	0.60 (0.38, 0.94)	0.02	**-40%**
Cardiac Arrest	11/1870 (0.6)	24/1823 (1.3)	0.44 (0.21, 0.89)	0.02	**-56%**



Gaba P. et Al, JACC May 2022

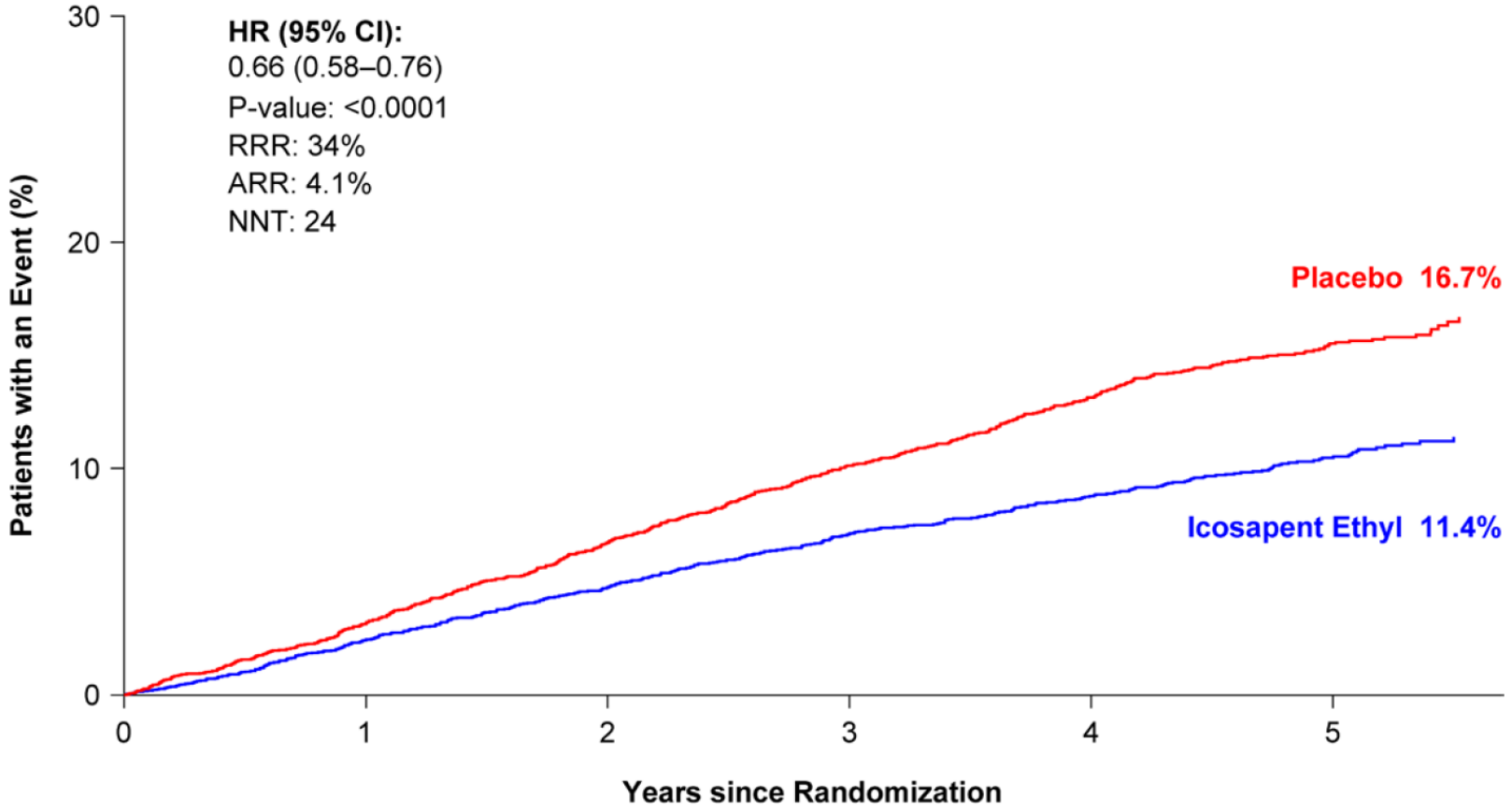
Time to First Event, Primary Composite Endpoint in Patients with Recent ACS <12 Months



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.

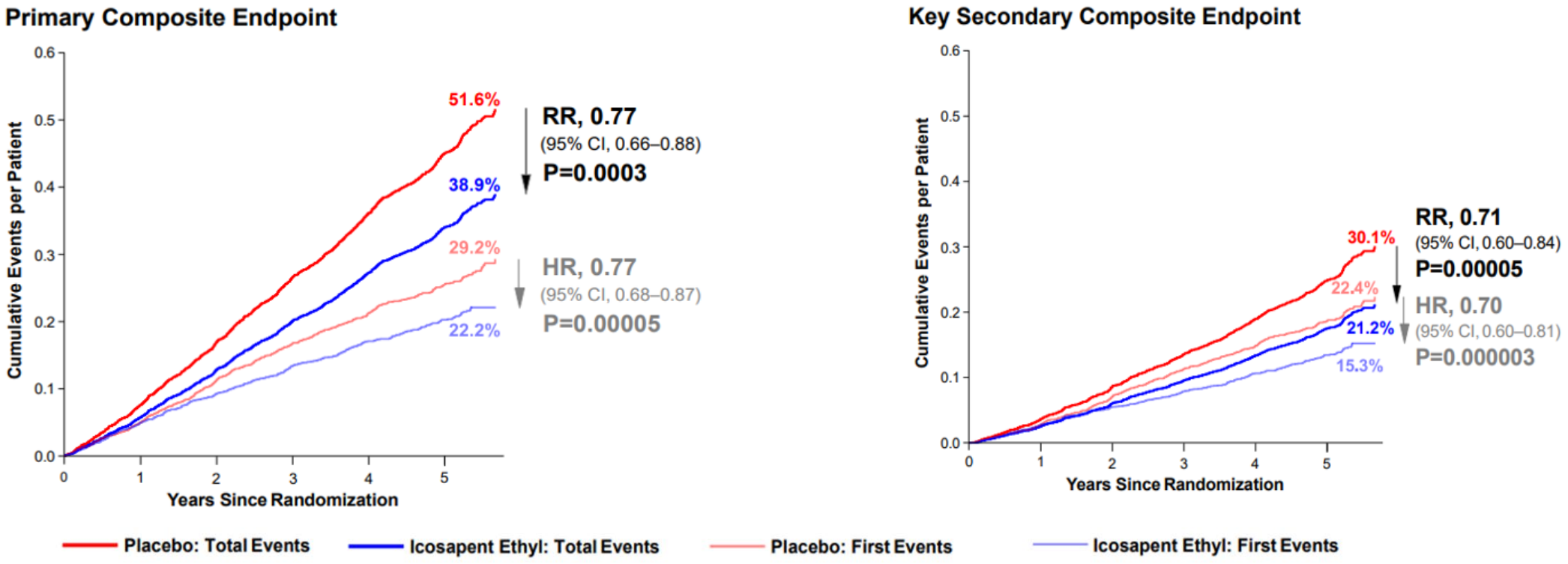
Reduction in Revascularization With Icosapent Ethyl



No. at Risk						
Placebo	4090	3793	3430	2926	2460	1431
Icosapent Ethyl	4089	3838	3529	3062	2621	1521

Peterson BE, Bhatt DL et al. Circulation 2021; 143:33-44

- **Patients with diabetes(4787): icosapent ethyl reduced first and total primary and secondary endpoints**



Bhatt DL. ADA 2020, virtual.

Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

Patients With TEAEs, n (%)	Icosapent Ethyl (N=4,089)	Placebo (N=4,090)	*P*-value
Diarrhea	367 (9.0)	453 (11.1)	0.002
Peripheral oedema	267 (6.5)	203 (5.0)	0.002
Constipation	221 (5.4)	149 (3.6)	<0.001
Atrial fibrillation	215 (5.3)	159 (3.9)	0.003
Anaemia	191 (4.7)	236 (5.8)	0.03

TEAE, treatment-emergent adverse event.

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

Atrial Fibrillation or Flutter

Patients With TEAEs, n (%)	Icosapent Ethyl (N=4,089)	Placebo (N=4,090)	*P*-value
Afib/Aflutter TEAEs and positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalisation	321 (7.9)	248 (6.1)	0.002
Afib/Aflutter TEAEs[a]	236 (5.8)	183 (4.5)	0.008
Serious Afib/Aflutter TEAEs[b]	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalisation[c]	127 (3.1)	84 (2.1)	0.004

Stratified Analysis of Time to First Onset of Atrial Fibrillation or Flutter from Date of Randomization by Subjects Without Atrial Fibrillation or Flutter History, ITT Population

Adverse Event	Icosapent Ethyl	Placebo	HR (95% CI)	*P*-value
No Atrial fibrillation or flutter history	81/3721 (2.2%)	60/3707 (1.6%)	1.3 (0.95, 1.86)	0.0913

Source: EMDAC FDA November 14, 2019

- Atrial fibrillation/flutter requiring hospitalization ≥24 hours was an adjudicated efficacy endpoint
- **Clinical consequences, including stroke, myocardial infarction, cardiac arrest, and sudden cardiac death were reduced in the overall intent-to-treat population, with consistent results in those with a history of atrial fibrillation at baseline**

[a]Includes atrial fibrillation/flutter TEAEs. [b]Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. [c]Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalisation clinical events by the Clinical Endpoint Committee. TEAE, treatment-emergent adverse event.

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

Treatment-Emergent Adverse Event of Interest: Bleeding[1,2]

Serious Bleeding Trended Toward an Increase, Rates Were Low With No Significant Increases in Hemorrhagic Stroke, CNS Bleeding, or GI Bleeding

Patients With TEAEs, n (%)	Icosapent Ethyl (N=4,089)	Placebo (N=4,090)	*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

CNS, central nervous system; GI, gastrointestinal; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

1. Bhatt DL, et al. *N Engl J Med* 2019;380:11-22. 2. FDA Advisory Committee, 2019.

ESC European Society of Cardiology
European Heart Journal (2025) 46, 4359–4378
https://doi.org/10.1093/eurheartj/ehaf190
ESC GUIDELINES

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

Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

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

Criteri di eligibilità e rimborsabilità

Indicazione autorizzata: [redacted] è indicato per ridurre il rischio di eventi cardiovascolari in pazienti adulti in trattamento con statine ad elevato rischio cardiovascolare e con trigliceridi elevati (≥ 150 mg/dL) e

- malattia cardiovascolare accertata o
- diabete e almeno un altro fattore di rischio cardiovascolare

Indicazione ammessa alla rimborsabilità: [redacted] è indicato per il trattamento di pazienti di età 18-80 anni con malattia cardiovascolare accertata e BMI ≥ 27 kg/m^2, in trattamento con statina ad alta potenza alla massima dose tollerata + ezetimibe, che abbiano raggiunto i livelli target di colesterolo LDL (< 70 mg/dL), e presentino ipertrigliceridemia residua (TG ≥ 200 mg/dL) non spiegabile da altre cause e confermata in almeno 3 determinazioni nonostante buona aderenza dietetica

Paziente in prevenzione CV secondaria per presenza di:

Malattia cardiovascolare: cardiopatia ischemica, IMA, rivascolarizzazione coronarica (BAC o angioplastica), malattia coronarica multivasale
Malattia cerebrovascolare: ictus, TIA, stenosi carotidea (≥50% con sintomi o ≥70%), rivascolarizzazione carotidea (TEA o angioplastica)
Arteriopatia periferica sintomatica, rivascolarizzazione aortoiliaca o periferica (chirurgica o angioplastica)

Piano terapeutico icosapent etile (link)

Specialisti che gestiscono la patologia nella pratica clinica

- **Cardiologo**
- **Internista / Geriatra**
- **Endocrinologo / Diabetologo**
- **Neurologo**
- **Chirurgo vascolare**

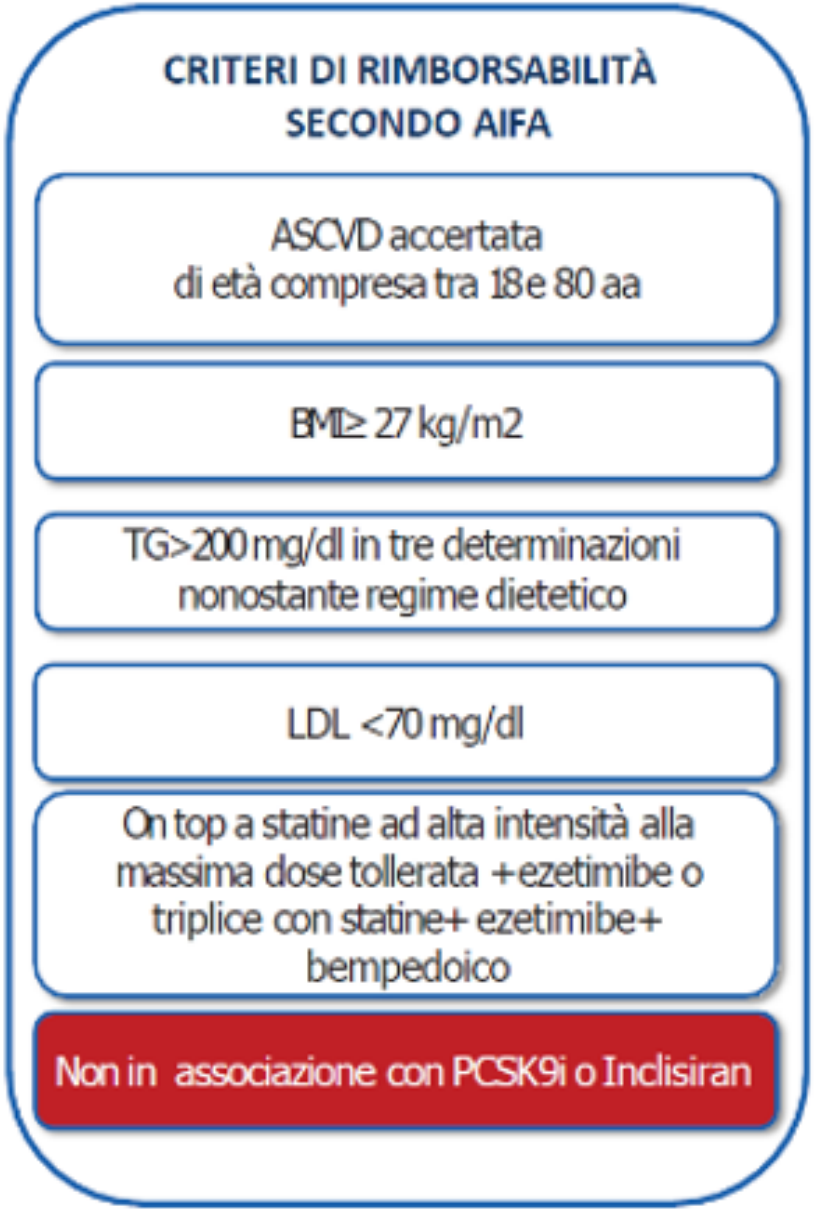
Determina AIFA n. 767/2024. G.U. Serie Generale n.293 del 14-12-2024

Registro AIFA

→RISCHIO CARDIOVASCOLARE

Associabile con FIBRATI

Associabile con ACIDO BEMPEDOICO



GRAZIE PER L’ATTENZIONE !!!

Ringraziamento : Dr. Paolo Fornengo