Riesgo cardiovascular residual de origen lipídico

… Más allá del LDL

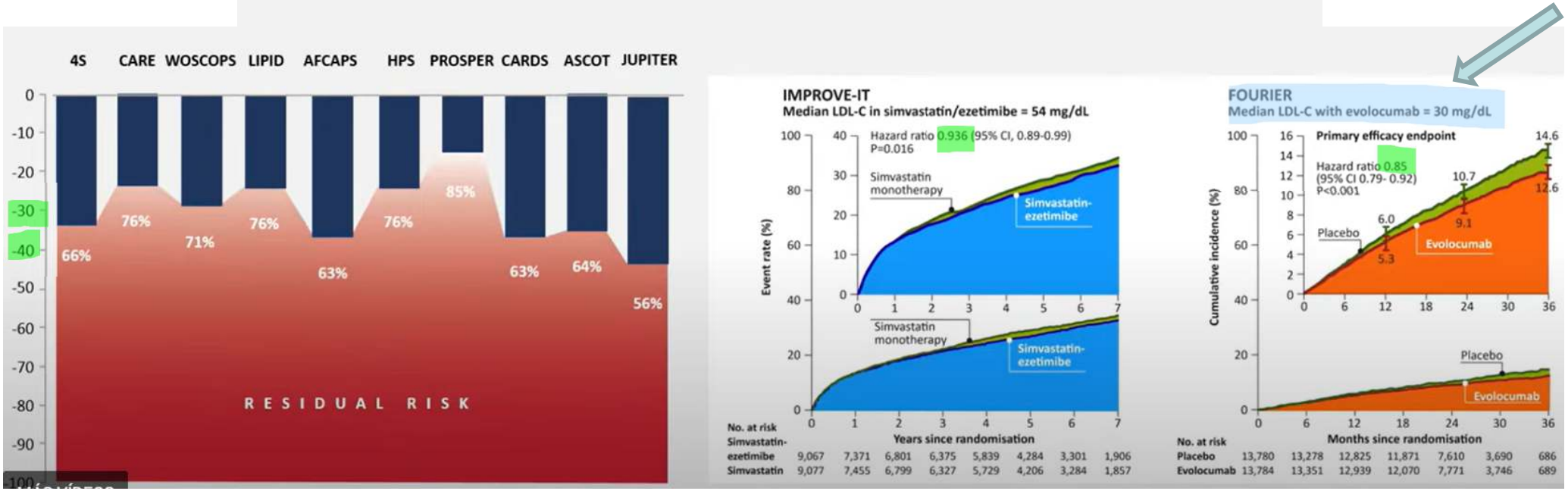
Christian Teijo Núñez
Hospital de León
14.04.2023

Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

Riesgo CV a pesar de reducir cLDL



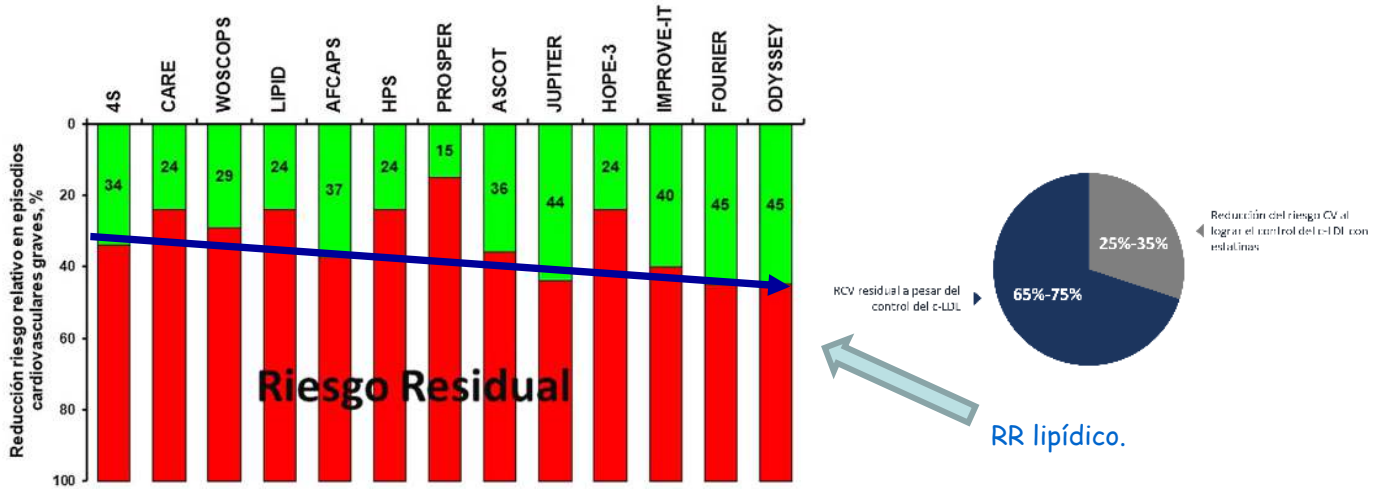


Figura 1 Reducción del riesgo relativo de episodios cardiovasculares graves y riesgo residual en los principales estudios de intervención con estatinas en monoterapia y combinadas con ezetimiba o inhibidores de PCSK9.

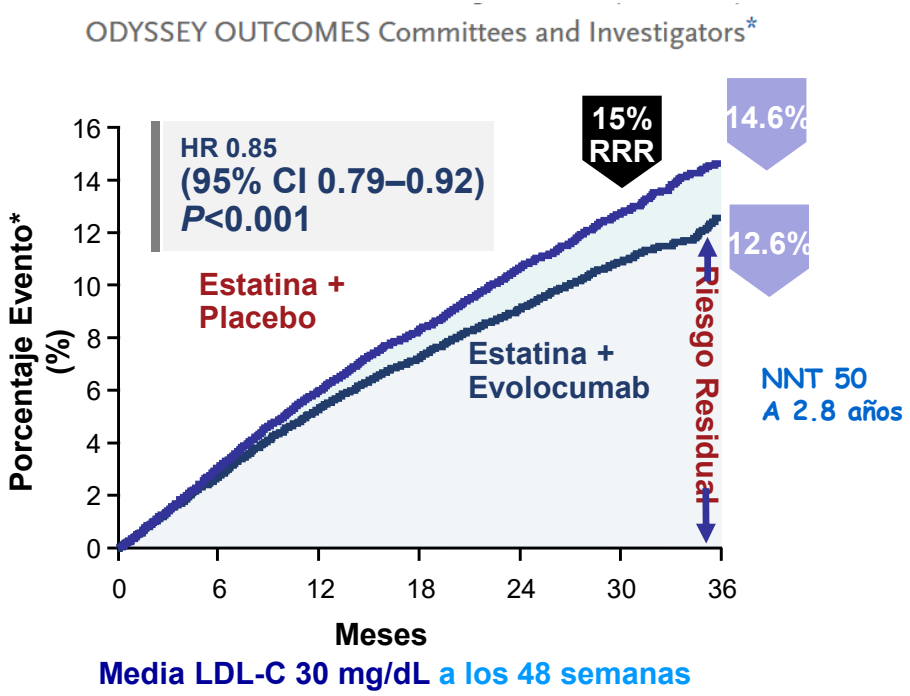
Junta de Castilla y León

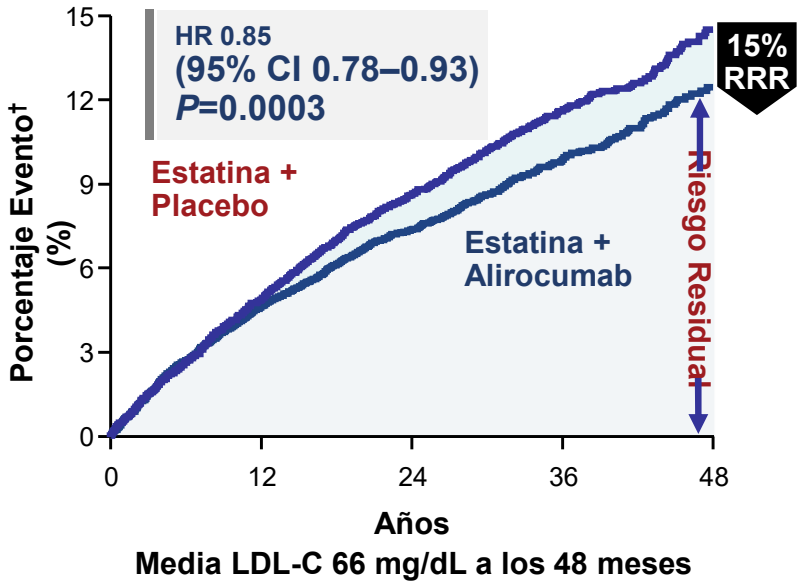
Sacyl

Complejo Asistencial Universitario de León

Riesgo CV residual es la suma de varios factores

El riesgo residual persiste a pesar de la reducción agresiva del LDL-C con inhibidores de PCSK9 [1,2]





1. Sabatine MS et al. *N Engl J Med.* 2017;376(18):1713-1722

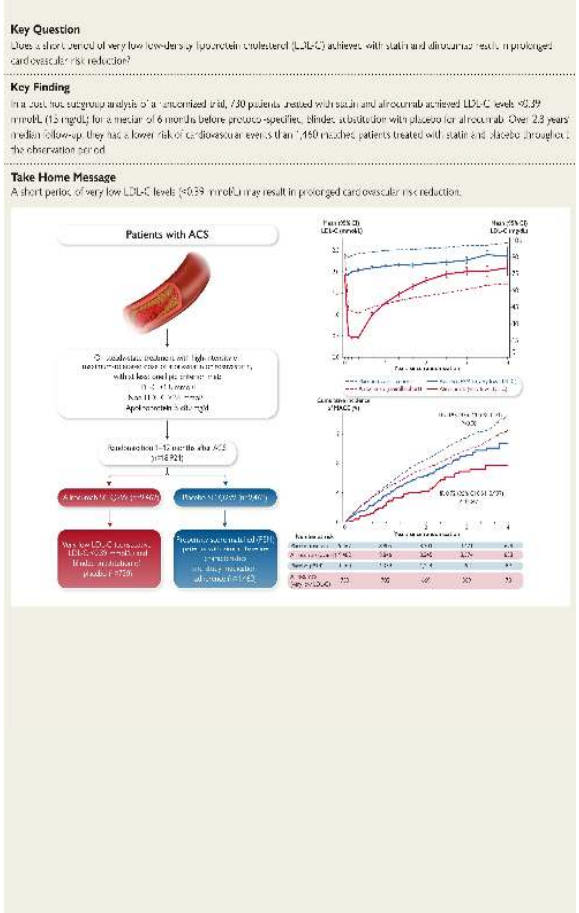
2. Schwartz GG et al. *N Engl J Med.* 2018;379(22):2097-2107.

RRR=reducción del riesgo relativo.
*Compuesto de muerte CV, IM, ictus, hospitalización por angina inestable o revascularización coronaria; (MACE 5 p.)
†Compuesto de muerte por enfermedad coronaria, IM no mortal, ictus isquémico mortal o no mortal, u hospitalización por angina inestable.
CV, cardiovascular; RRR, reduccion de riesgo relative; HR, hazard ratio; c-LDL, colesterol unido a lipoproteínas de baja densidad

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

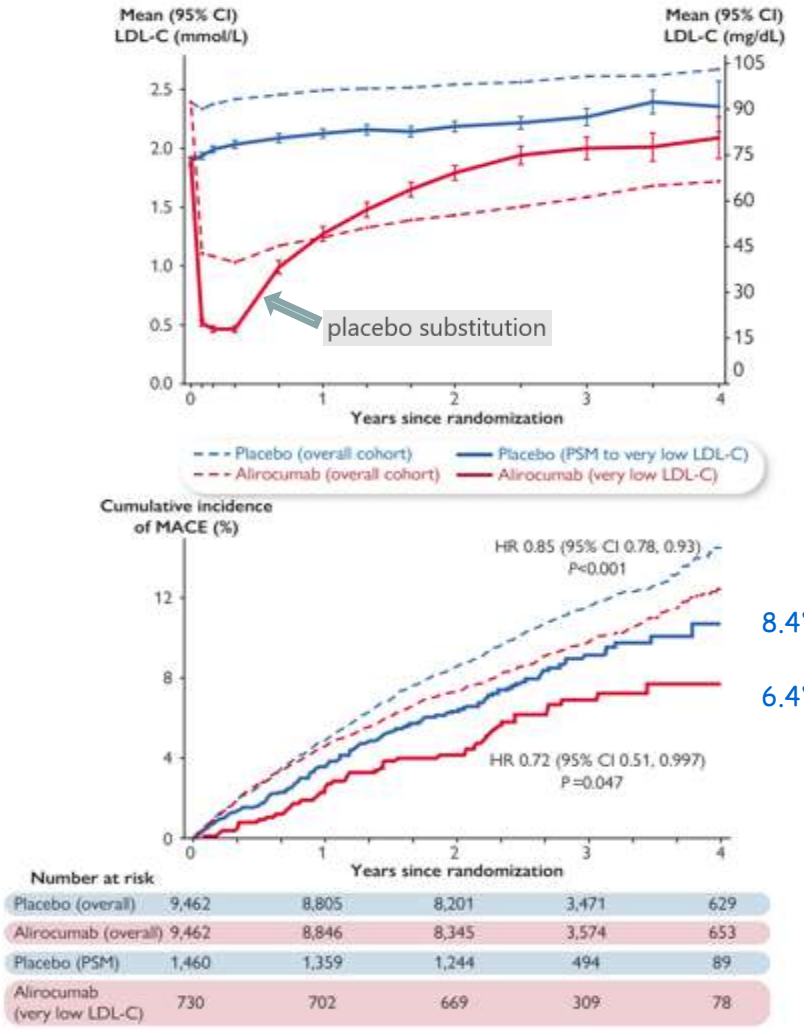
Transiently achieved very low LDL-cholesterol levels by statin and alirocumab after acute coronary syndrome are associated with cardiovascular risk reduction: the ODYSSEY OUTCOMES trial

ODYSSEY OUTCOMES
18924 pacientes post-SCA
FR: Post-SCA
Alirocumab vs placebo
Seguimiento: 2.8 años



c-LDL < 15 mg/dL durante 6 meses

730 Alirocumab vs 1460 placebo
2.8 años



8.4%

6.4%

NNT 50
A 2.8 años

Number at risk

Placebo (overall)	9,462	8,805	8,201	3,471	629
Alirocumab (overall)	9,462	8,846	8,345	3,574	653
Placebo (PSM)	1,460	1,359	1,244	494	89
Alirocumab (very low LDL-C)	730	702	669	309	78

Eur Heart J, ehad144, https://doi.org/10.1093/eurheartj/ehad144
Published: 05 March 2023

Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/561767/2020
EMEA/H/C/005333

Leqvio (*inclisiran*)

ARN interferente anti PCSK9

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/65186/2020
EMEA/H/C/004958

Nilemdo (*ácido bempedoico*)

Inhibidor adenosina trifosfato citrato liasa hepática

Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

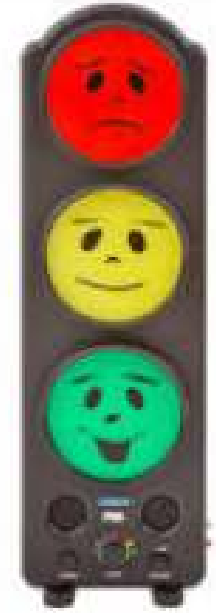
Riesgo CV residual es la suma de varios factores

ECV-establecida

Terapia con estatinas de alta intensidad

	Riesgo residual asociado al colesterol	Riesgo residual inflamatorio	Riesgo residual trombótico	Riesgo residual asociado a los TG
Alteración biológica				
Biomarcador fundamental	c-LDL- ≥100 mg/dl	PCRas ≥2 mg/l IL-6 elevada	No se dispone de un biomarcador único	TG ≥100 mg/dl
Posible intervención	Reducción dirigida de c-LDL	Reducción dirigida de la inflamación	Reducción dirigida de la trombosis	Reducción dirigida de los TG
Evidencias procedentes de los ensayos clínicos	Recommendation for anti-inflammatory therapy: Low-dose colchicine (0.5 mg o.d.) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.[85,86] — Class IIb, Level A — © ESC 2021		CHARISMA, PEGASUS COMPASS, THEMIS, THEMIS-PCI	AIM-HIGH and HPS2-THRIVE (Niacina) ACCORD PROMINENT REDUCE-IT STRENGTH

REDUCE-IT



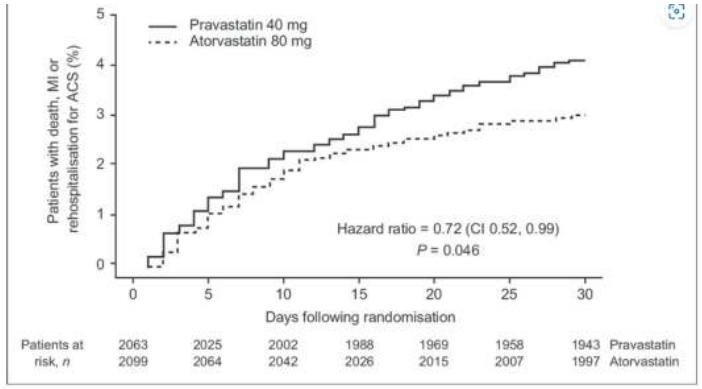
ECVA, enfermedad cardiovascular aterosclerótica; CV, cardiovascular; Lp (a), lipoproteína (a); c-LDL, colesterol unido a lipoproteínas de baja densidad; LoDoCo2, colchicina en dosis bajas; TG, triglicéridos.

Mason RP et al. *Arterioscler Thromb Vasc Biol*. 2020:40(5):1135-1147. + CTN

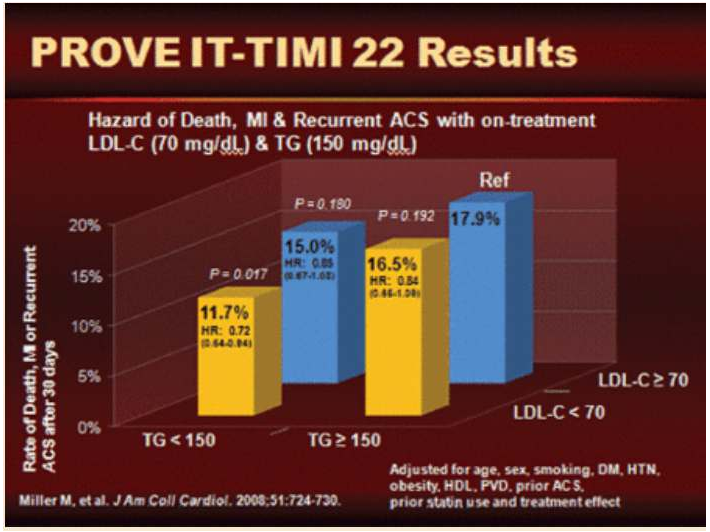
Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

Triglicéridos: ¿son o no son un factor de riesgo cardiovascular?

Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial



PROVE IT–TIMI 22: Kaplan–Meier estimates of the composite endpoint of death, myocardial infarction (MI), or rehospitalisation with recurrent acute coronary syndrome (ACS) by statin treatment (40 mg/day pravastatin or 80 mg/day atorvastatin), from randomisation to 30 days 6 Reprinted from J Am Coll Cardiol, Vol. 46, Ray et al., 6 ß



J Am Coll Cardiol. 2008 Feb 19;51(7):724-30.

Junta de Castilla y León

Lipids and cardiovascular disease 3

Triglycerides and cardiovascular disease

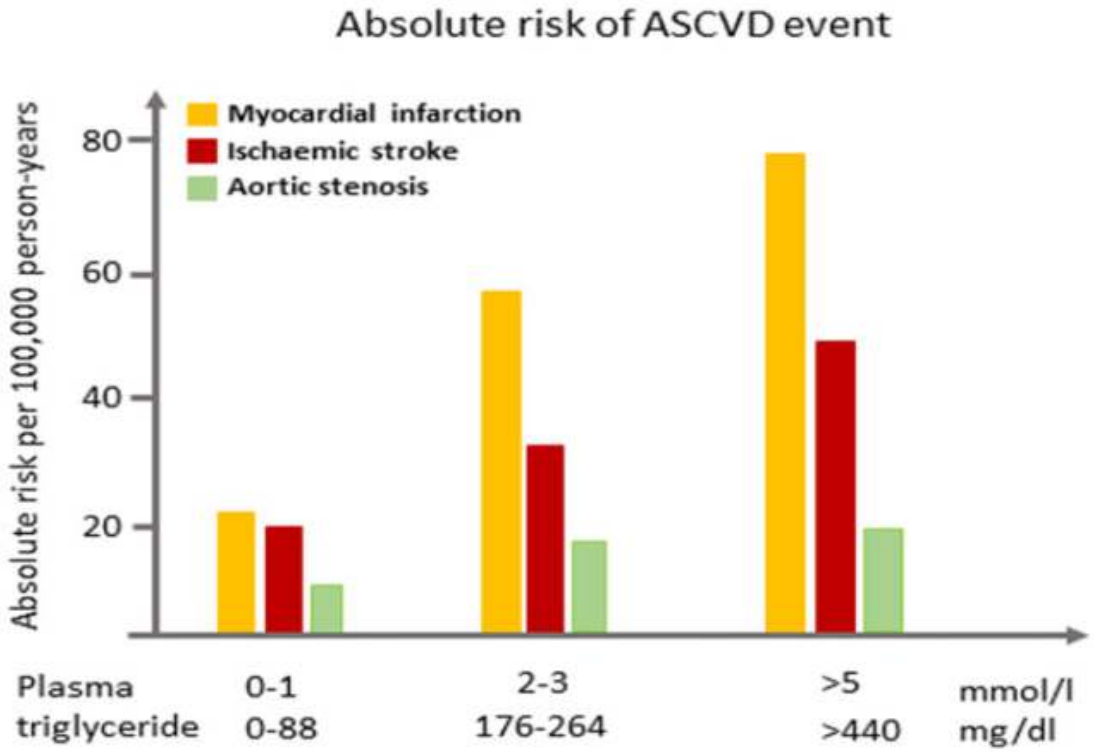


Figure 3 Absolute risk of cardiovascular morbidity as a function of increasing non-fasting plasma triglycerides in the general population. Based on data from more than 100 000 individuals in the Copenhagen General Population Study, as derived from refs.[11,17,27,28] ASCVD, atherosclerotic cardiovascular disease.

CHS: 106216 pac. 11 años.

THE LANCET Volume 384, Issue 9943, 16–22 August 2014, Pages 626-635

Sacyl

Complejo Asistencial Universitario de León

Copenhagen General Population Study (CGPS)
103,860 individuals
11% lipid-lowering therapy
baseline 2003-2014
2% heart failures

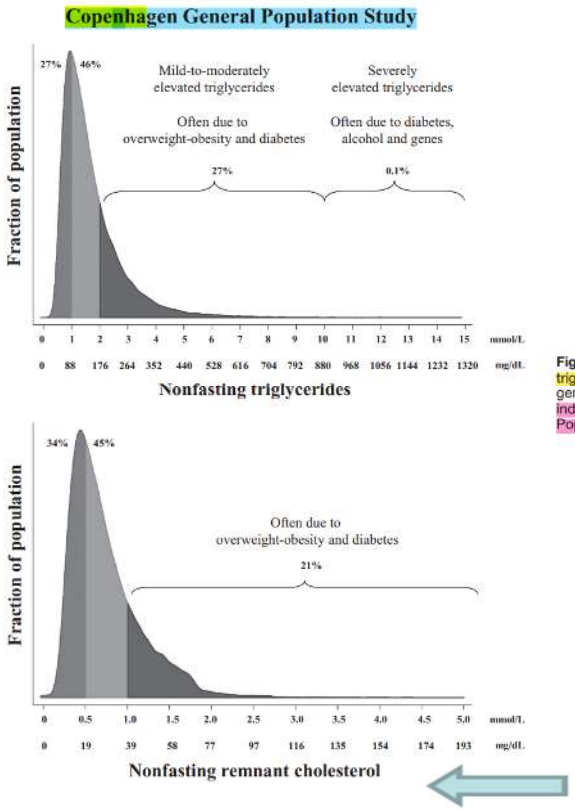
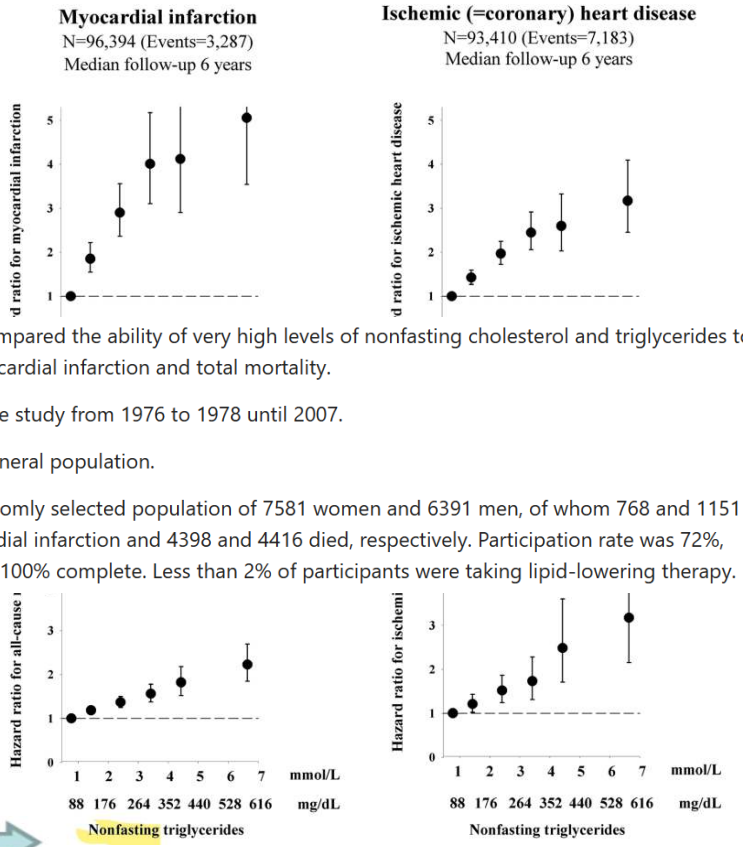


Figure 2. Distribution of nonfasting plasma triglycerides and remnant cholesterol in the general population. Distributions are from 84 177 individuals from the Copenhagen General Population Study.

Copenhagen City Heart Study and Copenhagen General Population Study



Objectives: We compared the ability of very high levels of nonfasting cholesterol and triglycerides to predict risk of myocardial infarction and total mortality.

Design: Prospective study from 1976 to 1978 until 2007.

Setting: Danish general population.

Participants: Randomly selected population of 7581 women and 6391 men, of whom 768 and 1151 developed myocardial infarction and 4398 and 4416 died, respectively. Participation rate was 72%, and follow-up was 100% complete. Less than 2% of participants were taking lipid-lowering therapy.

CV, cardiovascular; TG, triglicéridos.

Nordestgaard BG et al. *Circ Res*. 2016;118(4):547-563

Riesgo residual no dependiente de LDL

- TG:

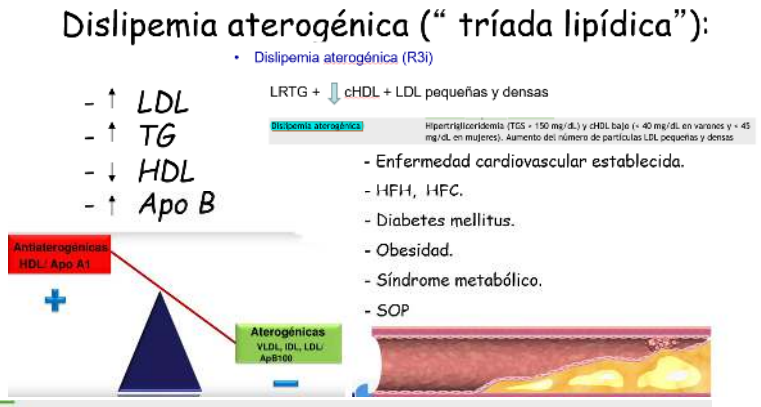
Hipertrigliceridemia	– TGS deseables < 150 mg/dL	
	– Hipertrigliceridemia:	
	– Leve: 150-499 mg/dL	: > RCV indep. LDL
	– Moderada 500-1.000 mg/dL	: FR Pancreatitis aguda
	– Grave: > 1.000 mg/dL	

LRTG y sus remanentes: QMr, VLDLr y IDL.

- HDL

- Dislipemia aterogénica (R3i)

LRTG + ⇩ cHDL + LDL pequeñas y densas



Dislipemia aterogénica	Hipertrigliceridemia (TGS > 150 mg/dL) y cHDL bajo (< 40 mg/dL en varones y < 45 mg/dL en mujeres). Aumento del número de partículas LDL pequeñas y densas

- Lp(a).

Remnant Cholesterol, Not LDL Cholesterol, Is Associated With Incident Cardiovascular Disease

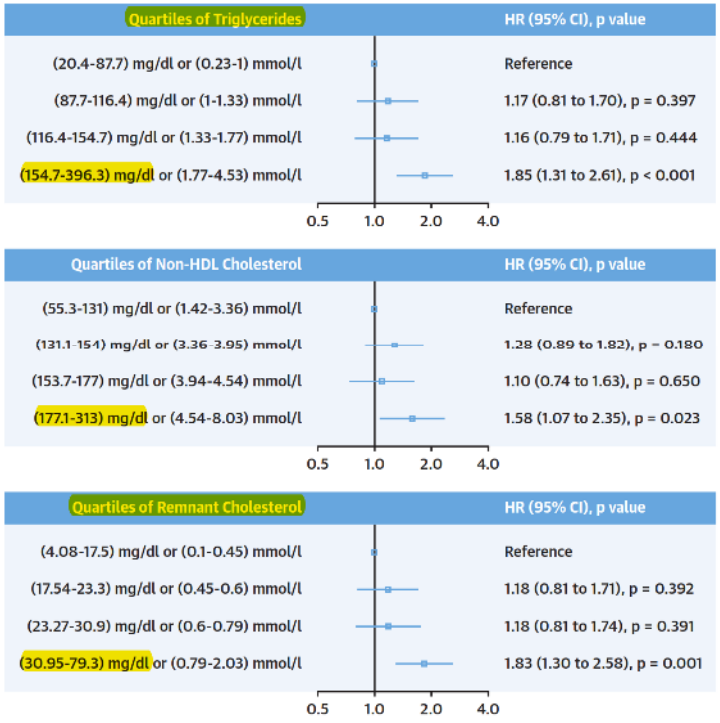
Olga Castañer, MD, PhD,[a,b] Xavier Pintó, MD, PhD,[b,c] Isaac Subirana, PhD,[d] Antonio J. Amor, MD, PhD,[b,e]

PREDIMED (Prevención con Dieta Mediterránea).
6901 en Prevención Primaria.
67 años.
48% DM
IMC 30.
4.8 años → 263 MACEs

TABLE 3 Association of Baseline Lipid Values With Cardiovascular Outcomes

	No Event (n = 6,638)	Event (n = 263)	Hazard Ratio (95% CI)	p Value
HDL-C, mg/dl	51.3 ± 11.5	49.1 ± 11.2	-5 mg/dl: 0.97 (0.91–1.04)	0.427
mmol/l	1.33 ± 0.29	1.27 ± 0.28		
LDL-C, mg/dl	130 ± 32.2	129 ± 32.5	-10 mg/dl: 1.01 (0.97–1.07)	0.583
mmol/l	3.36 ± 0.82	3.34 ± 0.83		
Triglycerides, mg/dl	128 ± 56.6	142 ± 66.3	+10 mg/dl: 1.04 (1.02–1.06)	<0.001
mmol/l	1.45 ± 0.64	1.60 ± 0.75		
Non–HDL-C, mg/dl	155 ± 34.1	157 ± 34.2	+10 mg/dl: 1.05 (1.01–1.10)	0.026
mmol/l	4.01 ± 0.87	4.06 ± 0.87		
Remnant-C, mg/dl	25.6 ± 11.3	28.5 ± 13.3	+10 mg/dl: 1.21 (1.03–1.33)	<0.001
mmol/l	0.66 ± 0.28	0.742 ± 0.34		
Triglycerides >150 mg/dl (1.71 mmol/l) + HDL-C <40/50 mg/dl (1.02/1.28 mmol/l) (in men/women)	915 (13.8)	48 (18.3)	1.44 (1.04–2.00)	0.030

FIGURE 2 Risk of MACEs Across Quartiles of Baseline Lipid Parameters



JACC VOL. 76, NO. 23, 2020
DECEMBER 8, 2020:2712-24

colesterol remanente (CR > 30)

Junta de Castilla y León

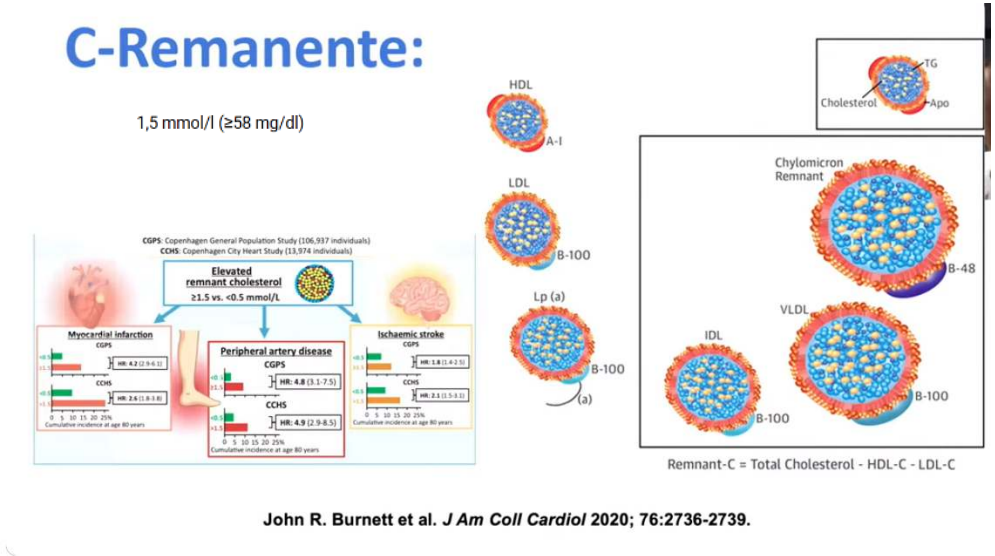
Sacyl

Complejo Asistencial Universitario de León

Diseño

Estudio prospectivo de cohorte de la población general danesa adulta (estudio de la población general de Copenhague)

CR – MACE – PS



John R. Burnett et al. *J Am Coll Cardiol* 2020; 76:2736-2739.

Tabla 1. MACE recurrentes por nivel de cuartil de colesterol remanente sin ayuno

	<0,5 mmol/l (<19 mg/dl) n = 793	0,5-0,99 mmol/l (19-38 mg/dl) n = 1400	1-1,49 mmol/l (39-57 mg/dl) n = 567	≥1,5 mmol/l (≥58 mg/dl) n = 213
MACE/1000 personas-año (95 % IC)				
Todos los pacientes	23 (19-27)	27 (24-31)	31 (26-37)	39 (30-50)
C-LDL <2,5 mmol/*	24 (19-30)	26 (22-31)	32 (25-42)	42 (29-61)
Cociente de riesgo (IC 95 %) de MACE recurrentes	Referencia	1,23 (0,98 - 1,55)	1,48 (1,14 - 1.92)	1,79 (1,28 - 2,49)

* o <97 mg/dl; C-LDL, colesterol de lipoproteína de baja densidad

En el caso de las personas con un diagnóstico de IM/ACV isquémico, se estimó un colesterol remanente más bajo de 0,8 mmol/dl (32 mg/dl) para reducir los MACE recurrentes en un 20 %

LRTG y sus remanentes: QMr, VLDLr y IDL.

Colesterol remanente: QMr+VLDLr+IDL : **CT** – cLDL – **CHDL**

CR > 30 mg/dL

Apo B-100 LP: VLDL, IDL, LDL y Lp(a)-Apo(a).

Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

Clínica e Investigación en Arteriosclerosis xxx (xxxx) xxx–xxx

04/2023

CLÍNICA E INVESTIGACIÓN EN
ARTERIOSCLEROSIS

www.elsevier.es/arterio

DOCUMENTO DE CONSENSO

Documento de consenso para la determinación e informe del perfil lipídico en laboratorios clínicos españoles ¿Qué parámetros debe incluir un perfil lipídico básico?☆

Tabla 2 Valores lipídicos deseables adultos según las Sociedades Europeas de cardiología, arteriosclerosis y medicina de laboratorio[17,18,3,6]

Parámetro	Valor deseable adultos
Colesterol total	< 200 mg/dL (5,17 mmol/L)
Colesterol-HDL	> 50 mg/dL mujeres (1,29 mmol/L) > 40 mg/dL hombres (1,03 mmol/L)
Colesterol no-HDL	Valores recomendados según el RCV • Prevención secundaria y RCV muy alto < 85 mg/dL (< 2,2 mmol/L) • RCV alto < 100 mg/dL (< 2,6 mmol/L) • RCV moderado < 130 mg/dL (< 3,.4 mmol/L)
Colesterol LDL	Valores recomendados según RCV • Prevención secundaria y RCV muy alto < 55 mg/dL (< 1,4 mmol/L) • RCV alto < 70 mg/dL (< 1,8 mmol/L) • RCV moderado < 100 mg/dL (< 2,6 mmol/L) • RCV bajo < 116 mg/dL (< 3 mmol/L)
Triglicéridos	TG < 150 mg/dL en ayunas (<1,69 mmol/L) (TG < 175 mg/dL no en ayunas) (<1,97 mmol/L)
Colesterol de partículas residuales	< 30 mg/dl (0,78 mmol/L) en ayunas < 30 mg/dl (0,91 mmol/L) no en ayunas
Apolipoproteína B	Valores recomendados según RCV • Prevención secundaria y RCV muy alto < 65 mg/dL (1,27 μmol/L) • RCV alto < 80 mg/dL (1,56 μmol/L) • RCV moderado < 100 mg/dL (1,95 μmol/L)
Lp(a)	< 50 mg/dL (< 105 nmol/L)

RCV: riesgo cardiovascular; Lp(a): lipoproteína a; HDL: lipoproteínas de alta densidad; LDL: lipoproteínas de baja densidad. Colesterol de partículas residuales = CT − c-LDL − c-HDL.

- TG

De la teoría ….

a la práctica…

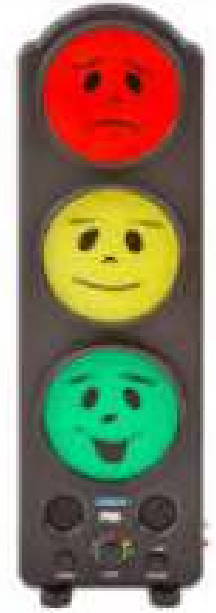
Riesgo CV residual es la suma de varios factores

ECV-establecida

Terapia con estatinas de alta intensidad

	Riesgo residual asociado al colesterol	Riesgo residual inflamatorio	Riesgo residual trombótico	Riesgo residual asociado a los TG
Alteración biológica				
Biomarcador fundamental	c-LDL- ≥100 mg/dl	PCRas ≥2 mg/l IL-6 elevada	No se dispone de un biomarcador único	TG ≥100 mg/dl
Posible intervención	Reducción dirigida de c-LDL	Reducción dirigida de la inflamación	Reducción dirigida de la trombosis	Reducción dirigida de los TG
Evidencias procedentes de los ensayos clínicos	IMPROVE-IT, FOURIER, SPIRE, ODYSSEY	CANTOS, COLCOT, LoDoCo2, CLEAR-Synergy Rescue /(-) IL-6/	CHARISMA, PEGASUS COMPASS, THEMIS, THEMIS-PCI	AIM-HIGH and HPS2-THRIVE (Niacina) ACCORD PROMINENT REDUCE-IT STRENGTH

REDUCE-IT



ECVA, enfermedad cardiovascular aterosclerótica; CV, cardiovascular; Lp (a), lipoproteína (a); c-LDL, colesterol unido a lipoproteínas de baja densidad; LoDoCo2, colchicina en dosis bajas; TG, triglicéridos.

Mason RP et al. *Arterioscler Thromb Vasc Biol*. 2020:40(5):1135-1147. + CTN

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

Fibratos

↑ c-HDL 10%–20%
↓ c-LDL 5%–20%
↓ Triglicéridos 20%–50%

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ACCORD lipid
5518 pacientes.
Alto RCV + D. Aterogénica (TG 240 mg/dl.)
SIMVA/FENOFIBRATO vs SIMVA/ Placebo
Seguimiento 4.7 años

ABSTRACT

METHODS

We randomly assigned 5518 patients with type 2 diabetes who were being treated with open-label simvastatin to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

CONCLUSIONS

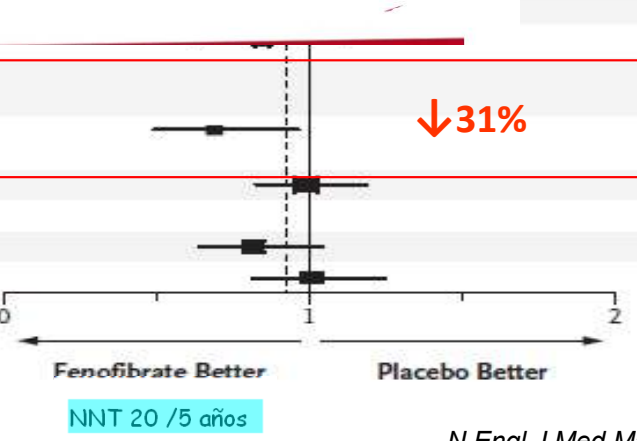
The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00000620.)

N Engl J Med March 14, 2010 online

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

↓ Triglicéridos 26%

Subgroup	Fenofibrate	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	% of events (no. in group)			
Overall				
Sex				0.01
Female				
Male				
Age				0.25
<65 yr				
≥65 yr				
Race				0.09
Nonwhite				
White				
Previous cardiovascular disease				0.45
No				
Yes				
Glycemia group				0.36
Standard therapy				
Intensive therapy				
LDL cholesterol				0.12
≤84 mg/dl				
85–111 mg/dl				
≥112 mg/dl				
HDL cholesterol				0.24
≤34 mg/dl				
35–40 mg/dl				
≥41 mg/dl				
Triglycerides				0.64
≤128 mg/dl				
129–203 mg/dl				
≥204 mg/dl				
Triglyceride–HDL cholesterol combination				0.06
Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl	12.37 (485)	17.32 (456)		
All others	10.11 (2264)	10.11 (2284)		
Glycated hemoglobin				0.20
≤8.0%	8.69 (1324)	10.56 (1335)		
≥8.1%	12.20 (1435)	11.94 (1415)		

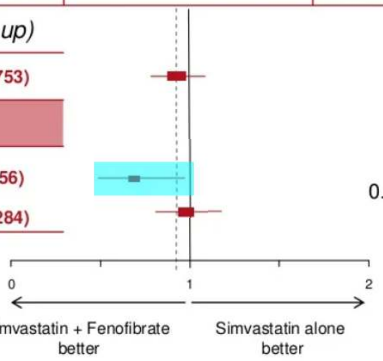


↓31%

NNT 20 /5 años

ACCORD Lipid
31% reducción en eventos en pacientes con Dislipidemia aterogénica

Subgroup	Simvastatin + Fenofibrate	Simvastatin + Placebo	Hazard ratio (95% CI)	*p* value for interaction
	% of event (no. in group)			
Overall	10.5 (2765)	11.3 (2753)		
Triglyceride – HDL-C combination				
TG ≥204 mg/dL + HDL-C ≤34 mg/dL	12.4 (485)	17.3 (456)		0.06
All others	10.1 (2264)	10.1 (2284)		



- Se necesita tratar 20 pacientes diabéticos tipo 2 y dislipidemia aterogénica por 5 años para prevenir 1 evento cardiovascular

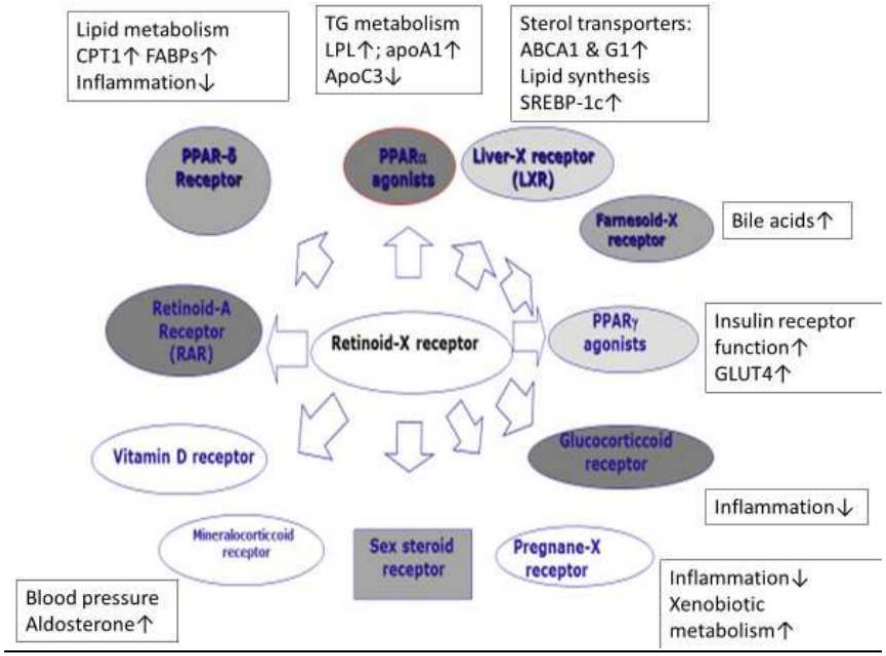
ACCORD Study Group. *N Engl J Med* March 14, 2010. Epub.

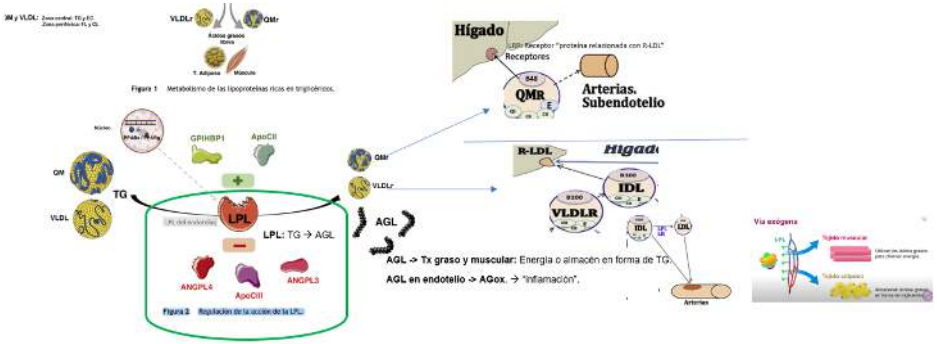
N Engl J Med March 14, 2010 online

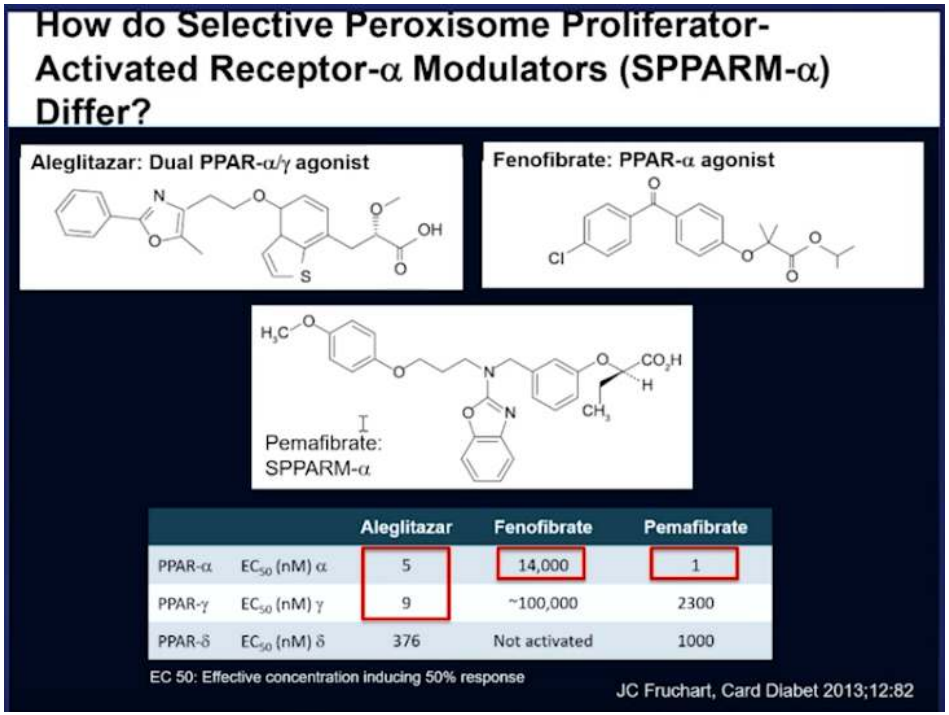
Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

Recommendations for drug treatments of patients with hypertriglyceridaemia.

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[534–536]	IIb	B





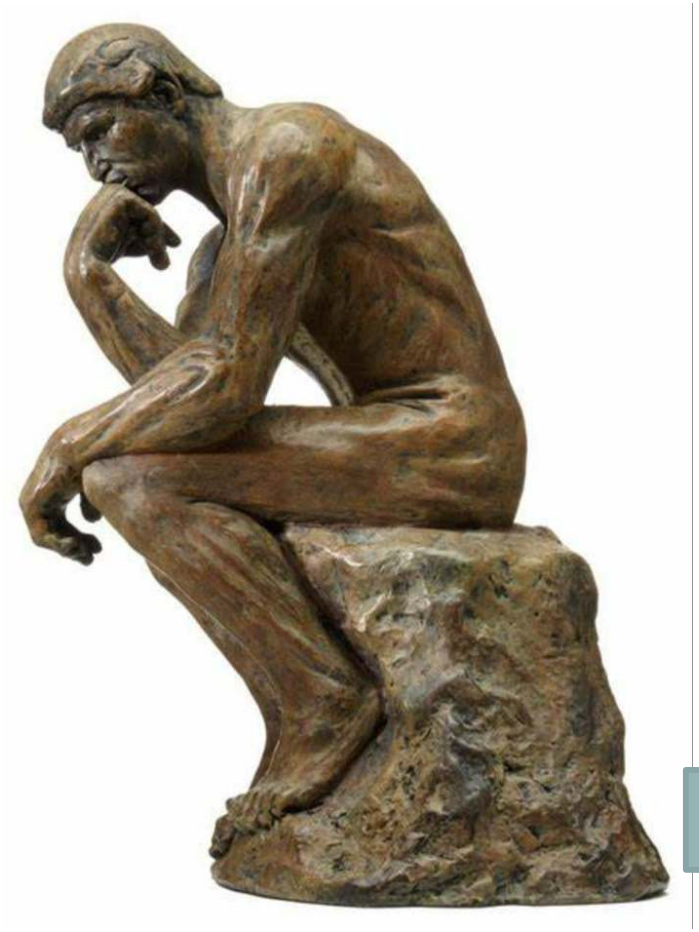


Wierzbicki AS, *et al. J Clin Pathol* 2022; 75:798–806. doi: 10.1136/jclinpath-2021-207719

Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León



Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

PROMINENT: Entry Criteria

Key Inclusion Criteria

Type 2 Diabetes

TG 200-499 and HDL-C ≤ 40 mg/dl

Established ASCVD (CAD, CeVD, or PAD)
or age ≥ 50 (M), ≥ 55 (F) years

Statin treatment
- Qualifying moderate or high intensity statin
- Other LLT with LDL ≤ 70 mg/dl
- Statin intolerance with LDL ≤ 100 mg/dl

- Total number of enrollees: 10,497
- Median duration of follow-up: 3.4 years
- Mean patient age: 64 years
- Percentage female: 28%
- Duration of diabetes ≥10 years: 46%

Baseline CV Medications and Lipid Levels

Patient characteristic	Placebo N = 5257		Pemafibrate N = 5240	
ACE inhibitor or ARB	4216	(80%)	4194	(80%)
Any Statin	5032	(96%)	5018	(96%)
High Intensity Statin*	3610	(69%)	3621	(69%)
Icosapent Ethyl	36	(1%)	48	(1%)
GLP-1 Analogue	479	(9%)	499	(10%)
SGLT2-Inhibitor	858	(17%)	881	(17%)
TG median (IQR) - mg/dl	269	(226, 338)	273	(227, 342)
HDL-C median (IQR) - mg/dl	33	(29, 37)	33	(29, 37)
LDL-C median (IQR) - mg/dl	78	(59, 102)	79	(60, 104)

Variable	Pemafibrate (N = 5240)	Placebo (N = 5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Triglyceride-related biomarkers			
Triglyceride level, measured			
Baseline — mg/dl	273 (227 to 342)	269 (226 to 338)	
4 Mo — mg/dl	189 (143 to 253)	254 (193 to 341)	
Median change from baseline — %	-31.1 (-48.9 to -9.6)	-6.9 (-28.4 to 20.2)	-26.2 (-28.4 to -24.10)
Remnant cholesterol level, measured			
Baseline — mg/dl	56 (43 to 73)	56 (43 to 72)	
4 Mo — mg/dl	30 (23 to 41)	44 (32 to 61)	
Median change from baseline — %	-43.6 (-57.8 to -24.1)	-20.2 (-38.3 to 3.8)	-25.6 (-27.3 to -24.0)

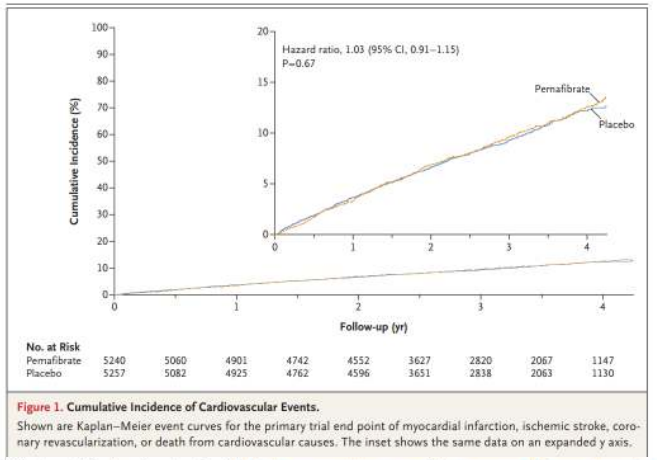


Figure 1. **Cumulative Incidence of Cardiovascular Events.**
Shown are Kaplan–Meier event curves for the primary trial end point of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. The inset shows the same data on an expanded y axis.

Side effects included high prevalence of venous thrombosis as well as renal events in the pemafibrate-treated group.

Event	Placebo	Pemafibrate	HR	95% CI
Biomarker Elevation				
- AST > 3X ULN	39	25	0.64	0.37-1.09
- ALT > 3X ULN	42	27	0.65	0.38-1.07
Physician-Reported Clinical Events				
- Any liver disease	265	219	0.83	0.69-0.99
- Non-alcoholic fatty liver disease	200	155	0.78	0.63-0.96

November 24, 2022
N Engl J Med 2022; 387:1923-1934
DOI: 10.1056/NEJMoa2210645

Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

Variable	Pemafibrate (N=5240)	Placebo (N=5257)	Treatment Effect†
	Median Value (IQR)		Mean % Change (95% CI)
Apolipoprotein B level, measured			
Baseline — mg/dl	90 (75 to 108)	89 (74 to 107)	
4 Mo — mg/dl	93 (77 to 111)	87 (73 to 105)	
Median change from baseline — %	-3.2 (−12.0 to 19.7)	−1.6 (−13.4 to 11.8)	4.8 (3.8 to 5.8)
LDL cholesterol level, measured			
Baseline — mg/dl	79 (60 to 104)	78 (59 to 102)	
4 Mo — mg/dl	91 (71 to 115)	80 (62 to 105)	
Median change from baseline — %	14.0 (−6.3 to 41.4)	2.9 (−13.5 to 24.6)	12.3 (10.7 to 14.0)

EDITORIAL FREE PREVIEW

The Fibrates Story — A Tepid End to a PROMINENT Drug

Salim S. Virani, M.D., Ph.D.

November 24, 2022
N Engl J Med 2022; 387:1991-1992
DOI: 10.1056/NEJMe2213208

Ongoing trials of agents that use alternative pathways to lower triglycerides and remnant cholesterol, including ApoCIII and angiopoietin-like protein 3 (ANGPTL3) inhibition, may help to clarify these issues.

EL SÍNDROME DE QUILOMICRONEMIA FAMILIAR (FCS

Tratamiento

La quilomicronemia no entraña un aumento del riesgo cardiovascular, y el objetivo del tratamiento será disminuir la concentración plasmática de triglicéridos lo suficiente para evitar los episodios de pancreatitis y que el paciente esté libre de síntomas. El tratamiento consiste en una

Clínica e Investigación en Arteriosclerosis 33 (2021) 1–6

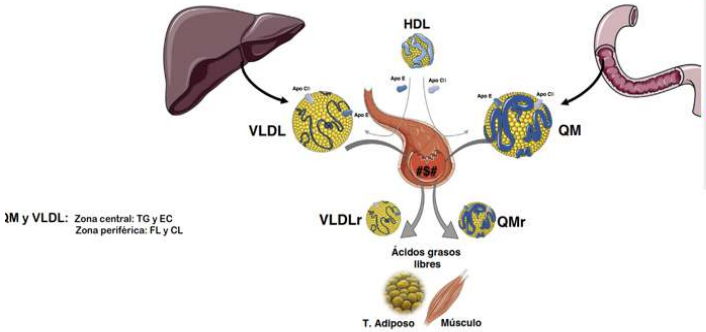


Figura 1 Metabolismo de las lipoproteínas ricas en triglicéridos.

Tabla 1 Lipoproteínas, tipos y composición

Lipoproteínas	Densidad (g/ml)	Diámetro (nm)	TG%	CE%	CL%	FL%	Apolipoproteínas	
							Principal	Otras
QM	< 0,95	80-100	90-95	2-4	1	2-6	apoB48	AI, AII, AIV, AV
VLDL	0,95-1,006	30-80	50-65	8-14	4-7	12-16	apoB100	AI, CII, CIII, AV
VLDLR e IDL	1,006-1,019	25-30	25-40	20-35	7-11	16-24	apoB100	CII, CIII, E
LDL	1,019-1,063	20-25	4-6	34-35	6-15	22-26	apoB100	
Lp(a)	1,006-1,125	25-30	4-8	35-46	6-9	17-24	apo(a)	B100
HDL	1,063-1,210	8-13	7	10-20	5	55	apoAI	AII, CIII, E, M

CE: colesterol esterificado; CL: colesterol libre; FL: fosfolípidos; HDL: *high density lipoproteins* (lipoproteínas de alta densidad); IDL: *intermediate density lipoproteins* (lipoproteínas de densidad intermedia); LDL: *low density lipoproteins* (lipoproteínas de baja densidad); Lp(a): lipoproteína (a); QM: quilomicrones; TG: triglicéridos; VLDL: *very low density lipoproteins* (lipoproteínas de muy baja densidad); VLDLR: *VLDL remnants* (remanentes de VLDL).

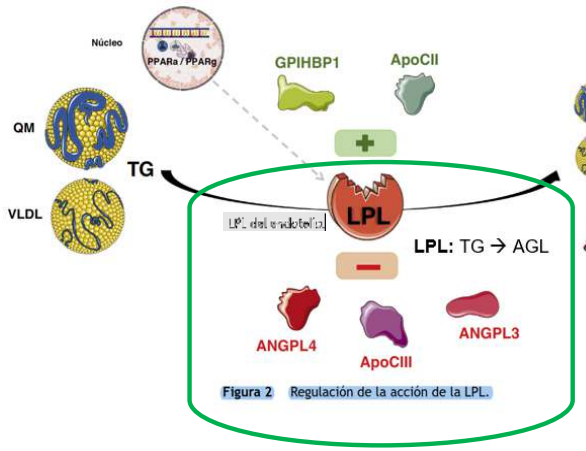
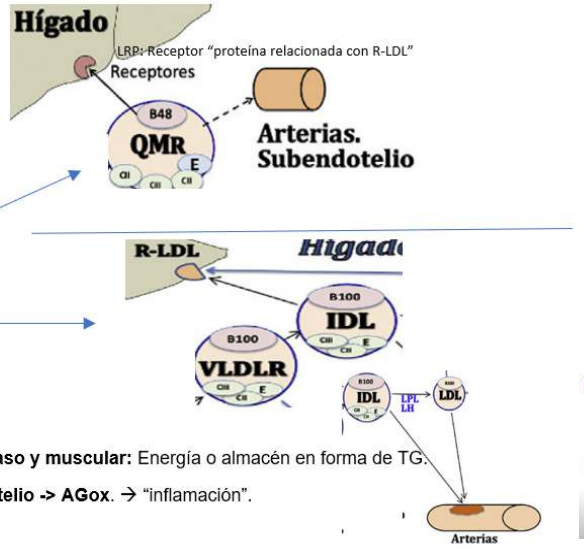


Figura 2 Regulación de la acción de la LPL.



AGL -> Tx graso y muscular: Energía o almacén en forma de TG.

AGL en endotelio -> AGox. → "inflamación".

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

ANGPTL3 inhibitors

ANGPTL3 (proteína 3 similar a la angiopoyetina)

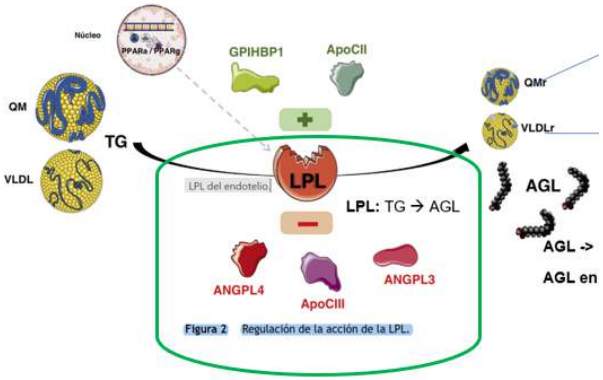


Table 2 Ongoing or recently completed studies involving inhibition of agents reducing triglyceride-rich lipoproteins

	Trial	Description
Pemafibrate	NCT03011450 (phase 3, in Europe) and NCT03001817 (phase 3, in US)	Study to evaluate the efficacy and safety of K-877 in adult patients with fasting high triglyceride levels and mild or moderate renal impairment
Evinacumab (mAb against ANGPTL3)	NCT04233918 (phase 3)	Evaluating the efficacy and safety of evinacumab in pediatric patients with homozygous familial hypercholesterolemia
	NCT03452228 (phase 2)	Safety and efficacy following repeat-dose of evinacumab (Anti-ANGPTL3) in patients with severe hypertriglyceridemia (sHTG) at risk for acute pancreatitis
	NCT03409744 (phase 3)	Evaluate the long-term safety and efficacy of evinacumab in patients with homozygous familial hypercholesterolemia
Vupanorsen (ANGPTL3-L_{Rx})	NCT04516291 (phase 2)	A dose-ranging study with vupanorsen (TRANSLATE-TIMI 70)
	NCT04459767 (phase 1)	Investigation of safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of vupanorsen in Japanese healthy adult participants with elevated triglycerides
ARO-ANG3 (silencing RNA)	NCT03747224 (phase 1)	Study of ARO-ANG3 in healthy volunteers and in dyslipidemic patients
AKCEA-APOCIII-L_{Rx}	NCT04568434 (phase 3)	A study of administered to patients with familial chylomicronemia syndrome (FCS) (BALANCE)
	NCT03385239 (phase 2)	Study of ISIS 678354 (AKCEA-APOCIII-LRx) in patients with hypertriglyceridemia and established cardiovascular disease (CVD)
ARO-APOC3 (silencing RNA)	NCT03783377 (phase 1)	Study of ARO-APOC3 in healthy volunteers, hypertriglyceridemic patients and patients with familial chylomicronemia syndrome (FCS)

Evinacumab for Homozygous Familial Hypercholesterolemia

Estudio ELIPSE HoFH

Table 2. Trial Outcomes at 24 Weeks.*

Outcome	Evinacumab (N=43)	Placebo (N=22)	LS Mean (±SE) Difference 95% CI
Primary outcome			
Percent change from baseline in LDL cholesterol	−47.1±4.6	1.9±6.5	−49.0±8.0 (−65.0 to −33.1)
Key secondary outcomes			
Percent change from baseline in apolipoprotein B	−41.4±3.3	−4.5±4.8	−36.9±5.9 (−48.6 to −25.2)
Percent change from baseline in non-HD lipoprotein cholesterol	−49.7±3.8	2.0±5.4	−51.7±6.6 (−64.8 to −38.5)
Percent change from baseline in total cholesterol	−47.4±3.0	1.0±4.2	−48.4±5.1 (−58.7 to −38.1)
Patients with ≥30% reduction from baseline in LDL cholesterol — no. (%)†	36 (84)	4 (18)	—
Patients with ≥50% reduction from baseline in LDL cholesterol — no. (%)†	24 (56)	1 (5)	—
Absolute change from baseline in calculated LDL cholesterol — mg/dl	−134.7±12.4	−2.6±17.6	−132.1±21.5 (−175.3 to −88.9)
Patients who met U.S. apheresis eligibility criteria — no. (%)†§	3 (7)	5 (23)	—
Patients with LDL cholesterol <100 mg/dl — no. (%)†	20 (47)	5 (23)	—
Patients who met EU apheresis eligibility criteria — no. (%)‖	14 (33)	17 (77)	—
Other secondary outcomes			
Percent change from baseline in triglycerides	−55.0±3.1	−4.6±7.0	−50.4±7.7 (−65.6 to −35.2)

Characteristic	Subcutaneous Evinacumab			Subcutaneous Placebo, Weekly (N=39)	Total (N=160)
	450 mg Weekly (N=40)	300 mg Weekly (N=42)	300 mg Every 2 Wk (N=39)		
Lipid-lowering therapy — no. (%)					
Any statin	24 (60)	24 (57)	24 (62)	27 (69)	99 (62)
High-intensity statin¶	17 (42)	21 (50)	14 (36)	19 (49)	71 (44)
Ezetimibe	7 (18)	15 (36)	12 (31)	14 (36)	48 (30)
PCSK9 inhibitor	40 (100)	42 (100)	39 (100)	39 (100)	160 (100)

1. NOMBRE DEL MEDICAMENTO

Evkeeza 150 mg/ml concentrado para solución para perfusión

EVKEEZA® (evinacumab-dgnb) injection, for intravenous use
Initial U.S. Approval: 2021

RECENT MAJOR CHANGES

Indications and Usage (1) 03/2023

INDICATIONS AND USAGE

EVKEEZA is an angiopoietin-like 3 (ANGPTL3) inhibitor indicated as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 5 years and older, with homozygous familial hypercholesterolemia (HoFH). (1)

Limitations of Use:

- The safety and effectiveness of EVKEEZA have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). (1)
- The effects of EVKEEZA on cardiovascular morbidity and mortality have not been determined. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage of EVKEEZA is 15 mg/kg administered by intravenous (IV) infusion once monthly (every 4 weeks). (2.1)

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

Riesgo CV residual es la suma de varios factores

ECV-establecida

Terapia con estatinas de alta intensidad

Alteración biológica	**Riesgo residual asociado al colesterol**	**Riesgo residual inflamatorio**	**Riesgo residual trombótico**	**Riesgo residual asociado a los TG**	
Biomarcador fundamental	**c-LDL- ≥100 mg/dl**	**PCRas ≥2 mg/l** **IL-6 elevada**	**No se dispone de un biomarcador único**	**TG ≥100 mg/dl**	
Posible intervención	**Reducción dirigida de c-LDL**	**Reducción dirigida de la inflamación**	**Reducción dirigida de la trombosis**	**Reducción dirigida de los TG**	**Re**
Evidencias procedentes de los ensayos clínicos	**IMPROVE-IT, FOURIER, SPIRE, ODYSSEY**	**CANTOS, COLCOT, LoDoCo2, CLEAR-Synergy Rescue /(-) IL-6/**	**CHARISMA, PEGASUS COMPASS, THEMIS, THEMIS-PCI**	**AIM-HIGH and HPS2-THRIV (Niacina)** **ACCORD** **PROMINENT** Inhbidores ANGPTL3 y APOIII ??? JELIS STRENGTH REDUCE-IT	

REDUCE-IT

ECVA, enfermedad cardiovascular aterosclerótica; CV, cardiovascular; Lp (a), lipoproteína (a); c-LDL, colesterol unido a lipoproteínas de baja densidad; LoDoCo2, colchicina en dosis bajas; TG, triglicéridos.

Mason RP et al. *Arterioscler Thromb Vasc Biol*. 2020:40(5):1135-1147. + CTN

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

Comparative Study > Atherosclerosis. 2003 Feb;166(2):351-7.
doi: 10.1016/s0021-9150(02)00364-7.

Low incidence of cardiovascular disease among the Inuit--what is the evidence?

Inuit = Esquimales groenlandeses

Omega-3 (n-3) y omega-6 (n-6)

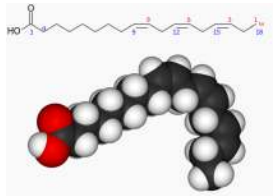
2 ácidos grasos "esenciales".

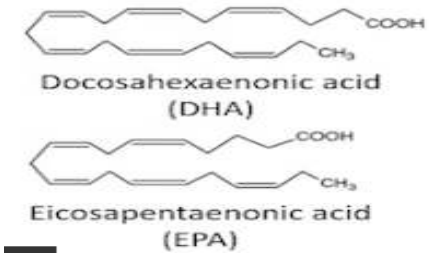
- ácido linoleico (AL), un ácido graso omega-6.
- ácido alfa-linolénico (ALA), un ácido graso omega-3.

.. Única fuente: DIETA

Fuentes alfa-linolénico (ALA):
Nueces, aceites vegetales de linaza, colza, soja y lino.

El **ácido α-linolénico** (ALA)





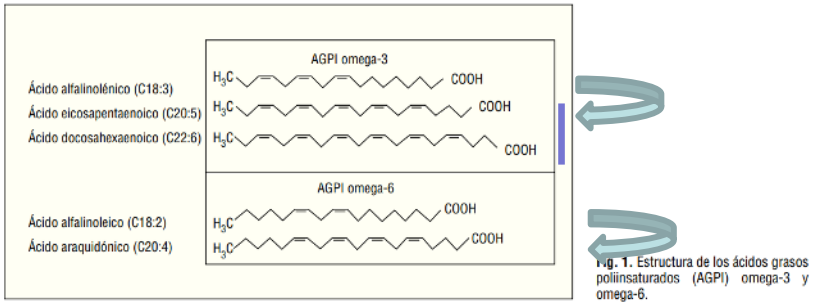


Fig. 1. Estructura de los ácidos grasos poliinsaturados (AGPI) omega-3 y omega-6.

Fuentes alfa-linoléico:
· verduras, frutas, frutos secos, cereales

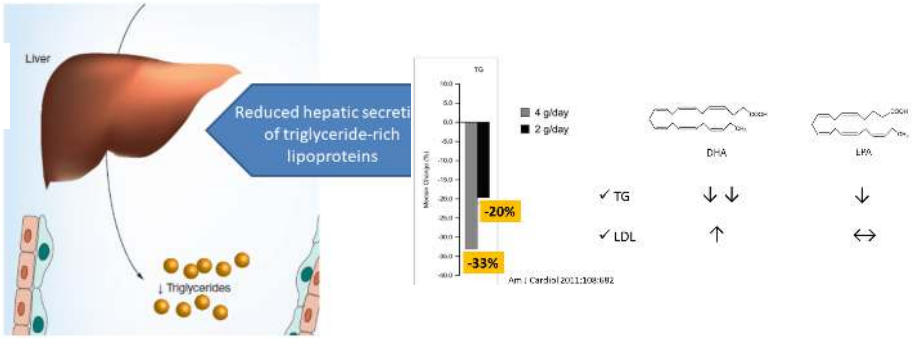
Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

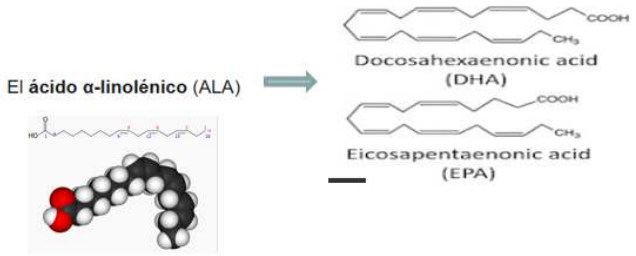
Acciones AG PI omega-3

↓TG



- Reducen síntesis hepática de triglicéridos y VLDL.
- (-) acil-CoA:1,2-diaglicerol aciltransferasa que interviene en la síntesis de TG.
- Reducen síntesis y secreción de QM.
- Acelera el aclaramiento postpandrial de los TG.

Nat Rev Cardiol. 2019; 2019;16:389-406



ELSEVIER

Atherosclerosis 200 (2008) 135–140

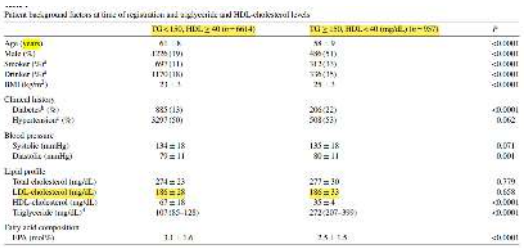
ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)

JELIS – POBLACIÓN JAPONESA
14981 pacientes
P. Primaria
EPA + ESTATINA vs Placebo + ESTATINA
Seguimiento 4.6 años
TG media 150 mg/dL. 50% TG normales.

↓ Triglicéridos 9%



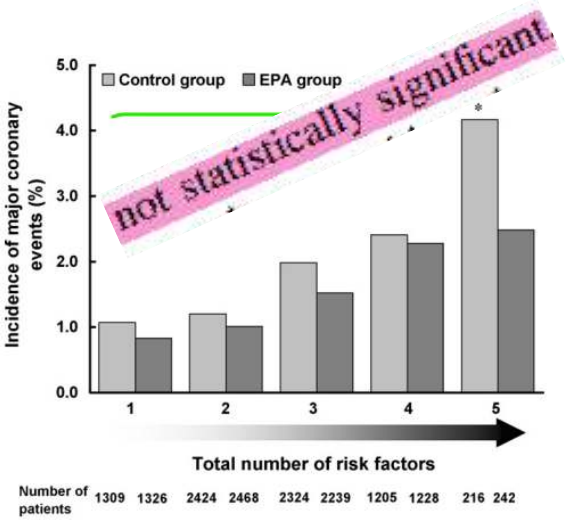


Fig. 1. Multiple risk factors and the incidence of MCE. Number of risk factors at the time of registration was counted: Risk A, hypercholesterolemia (all patients); Risk B, body mass index (BMI) ≥25; Risk C, triglyceride ≥150 mg/dL or HDL-cholesterol <40 mg/dL; Risk D, diabetes; Risk E, hypertension. The Cox proportional hazard model was adjusted for age, gender, smoking. $^{*}P<0.05$ vs. risk number 1 in the control group.

The primary endpoint was major coronary events (MCE), comprising: sudden cardiac death; fatal myocardial infarction; nonfatal myocardial infarction; unstable angina pectoris including hospitalization for documented ischemic episodes; and angioplasty/stenting or coronary artery bypass grafting.

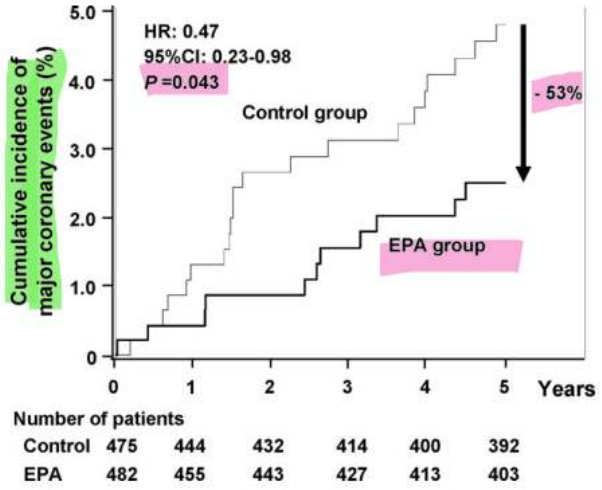


Fig. 3. Effects of EPA on the incidence of MCE for the high TG/low HDL-C

Primary endpoint

Major coronary events

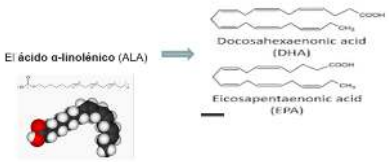
Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

STRENGTH (EPA plus DHA)

STRENGTH
13078 pacientes
Alto RCV + D. Aterogénica (TG 240 mg/dl.)
EPA/**DHA** 4 g. vs Placebo
Seguimiento 5 años

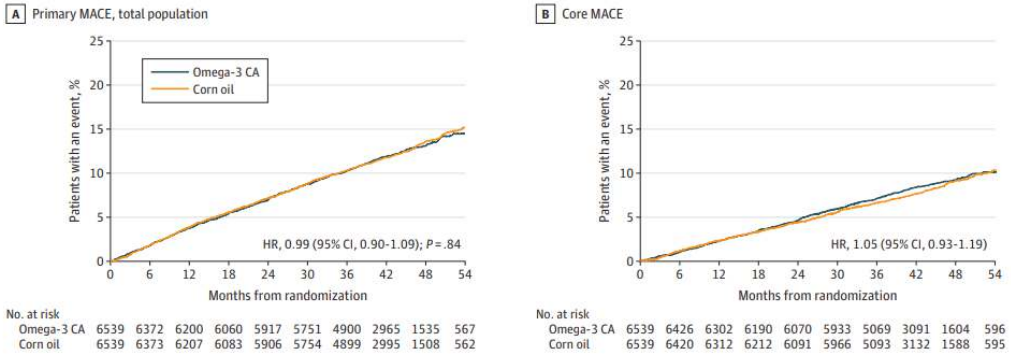


OBJECTIVE To determine the effects on cardiovascular outcomes of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with documented favorable effects on lipid and inflammatory markers in patients with atherogenic dyslipidemia and high cardiovascular risk.

OMACOR ®:2-4 g/día. ((EPA + ácido docosahexanóico (DHA))

Inicio del estudio: LDL-C fue de 76 mg/dl, HDL-C 36 mg/dl y TG 240 mg/dl.

Figure 2. Time to First Incidence of Any Component of the Primary Composite End Point and Time to Core MACE **MACE 5 p.**



A, The primary composite end point consisted of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina. Median (Q1-Q3) observation time was 41.3 (36.0-47.5) months for patients receiving omega-3 CA and 41.4 (35.9-47.4) months for patients receiving corn oil. B, Core major adverse cardiovascular events (MACE) included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Median (Q1-Q3) observation time of 41.5 (36.6-47.8) months for patients receiving omega-3 CA and 41.6 (36.8-47.4) months for patients receiving corn oil.

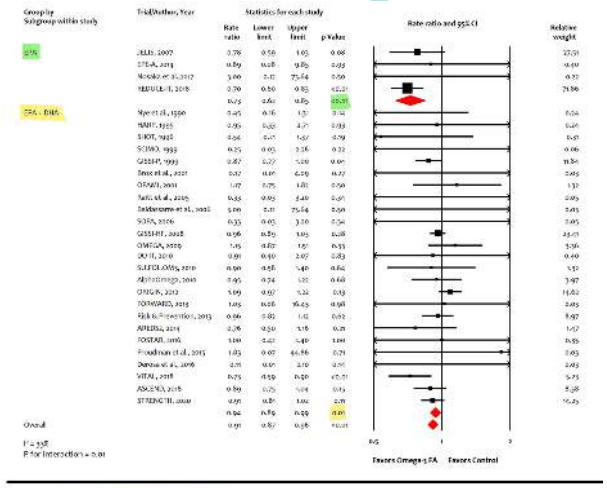
Prematurely stopped due to the low probability of demonstrating a clinical benefit despite a significant reduction in TG levels by 19%.

JAMA. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258
Published online November 15, 2020. Corrected on December 18, 2020.

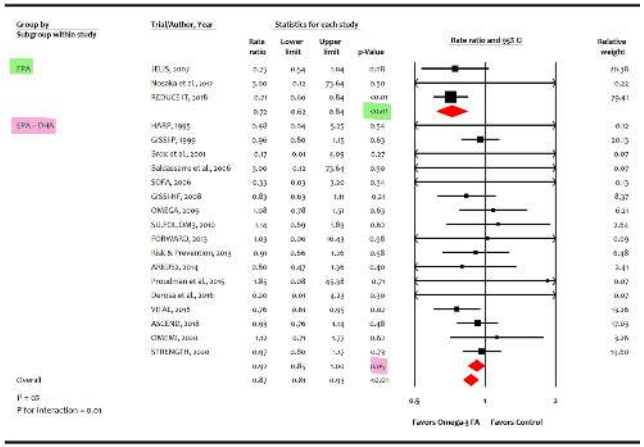
Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León

Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis

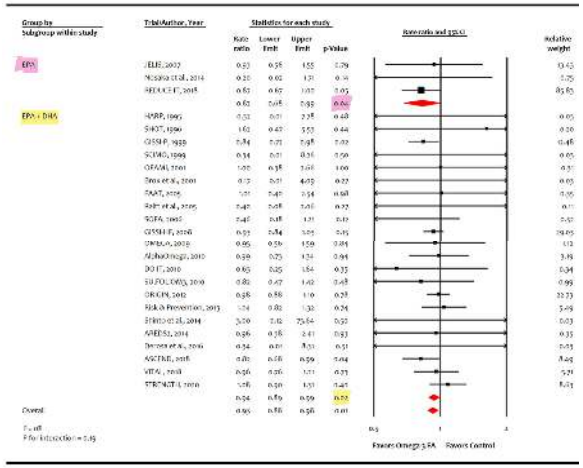
META
149051 pacientes
38 estudios RC
EPA vs EPA/ DHA
Seguimiento 4.9 años



. Effect of omega-3 fatty acid on coronary heart disease events.



Effect of omega-3 fatty acid on non-fatal myocardial infarction.



. Effect of omega-3 fatty acid on cardiovascular mortality.

Interpretation

Omega-3 FAs reduced cardiovascular mortality and improved cardiovascular outcomes. The cardiovascular risk reduction was more prominent with EPA monotherapy than with EPA+DHA.

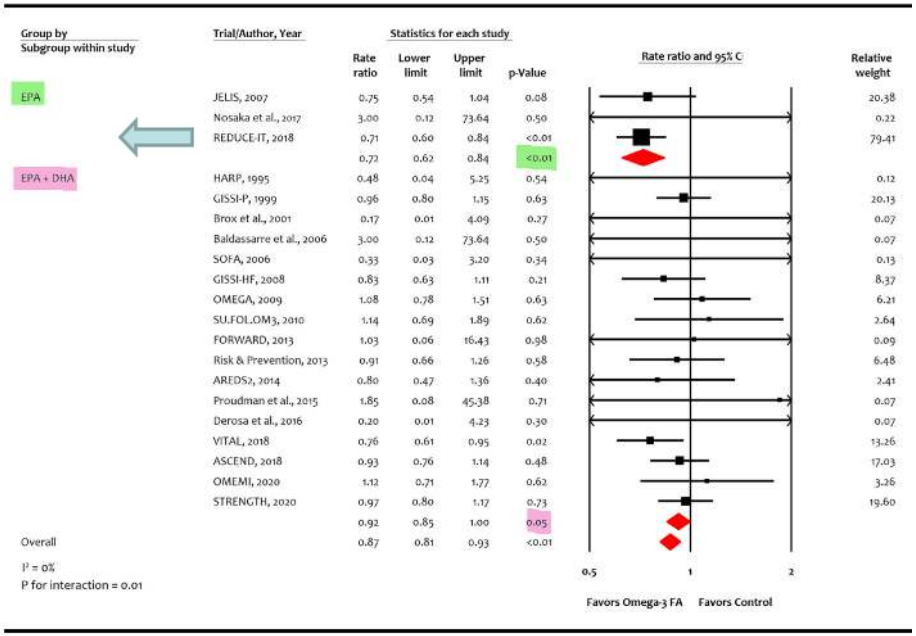
Junta de Castilla y León

Sacyl

Table 1
Baseline characteristics of trials and participants.

Trial/Author, y	Age, y	No. (%) Women	Coronary artery disease	Hypertension	Diabetes	Treatment	Patients	Dose, g/day	Baseline levels, mg/dL TG	LDL-C	Control
Alpha Omega, 2010[35]	69	504 (20.8)	2,428 (100)	NR	511 (21)	EPA + DHA	2404	0.4	144.3	101.5	Alpha linoleic acid
AFFORD, 2013[36]	61	105 (31.6)	43 (13.6)	146 (43.5)	26 (8.2)	EPA + DHA	165	2.40	—	—	Safflower oil
AREDS2, 2014[37]	74.3	2,387 (56.8)	405 (9.5)	—	546 (13)	EPA + DHA	2147	1.0	—	—	*Supplements
ASCEND, 2018[3]	63.3	5,796 (37.4)	0	9536 (62.6)	15.480 (100)	EPA + DHA	7740	0.84	—	113	Olive oil
Brox et al., 2001[38]	55	60 (50)	0	—	0	EPA + DHA	80	3.0	—	—	No treatment
Baldassarre et al., 2006[39]	53.7	6 (9.4)	0	0	0	EPA + DHA	32	1.8	276.1	154.4	Olive oil
DO IT, 2010[40]	70	0	0	157 (28)	82 (14.5)	EPA + DHA	282	1.32	150.4	158.3	Corn oil
Derosa et al., 2016[41]	54.1	141 (50.1)	—	—	0	EPA + DHA	138	2.55	182.5	127.5	No treatment
EPIC-1, 2008[42]	39.4	201 (55.4)	—	—	—	EPA + DHA	188	3.0	—	—	Medium chain triglycerides
EPE-A, 2014[43]	48.7	148 (60.9)	0	—	85 (35)	EPA	168	2.7	149	111	No treatment
ENRGISE, 2018[44]	77.6	137 (47.4)	—	200 (69.2)	68 (23.5)	EPA + DHA	148	1.8	—	—	Corn oil
FAAT, 2005[45]	65.5	68 (16.9)	314 (78.1)	—	—	EPA + DHA	200	2.6	—	—	Olive oil
FORWARD, 2013[46]	66.1	265 (45.2)	67 (11.7)	536 (91.5)	74 (12.9)	EPA + DHA	289	0.85	—	—	Olive oil
FOSTAR, 2016[47]	61	100 (50)	—	—	—	EPA + DHA	101	4.5	—	—	Sunola oil
GISSI-P, 1999[48]	59.4	854 (15.1)	5,664 (100)	4025 (35.5)	831 (14.6)	EPA + DHA	5666	0.87	162.6	137.3	No treatment
GISSI-HF, 2008[19]	67	1,516 (21.7)	3,467 (49.7)	3808 (54.6)	1,974 (28.3)	EPA + DHA	3494	0.87	—	—	Olive oil
HARP, 1995[49]	62	5 (6.5)	80 (100)	34 (42.2)	8 (13.6)	EPA + DHA	41	0.4	128	122	Olive oil
HEARTS, 2017[50]	63.0	208 (85)	240 (100)	206 (84)	68 (28.3)	EPA + DHA	143	3.36	123.0	78.5	No treatment
JELIS, 2007[2]	61	12,786 (68.6)	—	6619 (35.5)	3,040 (16)	EPA	9326	1.8	153.1	181.1	No treatment
Kumar et al., 2012[51]	62	141 (77.5)	31 (17.4)	95 (51.2)	27 (15.2)	EPA + DHA	92	1.7	—	—	No treatment
MAPT, 2017[52]	75.3	978 (64)	—	—	—	EPA + DHA	840	1.03	—	—	Paraffin oil
Nye, 1990[53]	54	17 (23)	73 (100)	—	—	EPA + DHA	36	3.6	—	—	Olive oil
Nosaka et al., 2017[54]	70.5	56 (23.5)	238 (100)	167 (70)	92 (38.7)	EPA	119	1.8	117	118	No treatment
OFAMI, 2001[55]	64	62 (26.1)	238 (100)	78 (26)	31 (10.4)	EPA + DHA	150	3.36	145.1	—	Corn oil
ORIGIN, 2012[56]	63.5	4,386 (35)	—	9962 (79.5)	—	EPA + DHA	6281	0.84	142	112	Olive oil
OMEGA, 2009[57]	64	977 (25.6)	3,818 (100)	2561 (66.5)	1,032 (27)	EPA + DHA	1940	0.85	—	—	Olive oil
OMEMI, 2020[7]	74	294 (29)	1,014 (100)	611 (60.3)	210 (20.7)	EPA + DHA	505	1.59	115.4	75.1	Corn oil
Proudman et al., 2015[58]	55.8	101 (72.7)	—	—	—	EPA + DHA	87	5.5	—	—	Sunola/ capelin oil
Raitt et al., 2005[59]	62.5	28 (14)	146 (73)	101 (50.5)	47 (23.5)	EPA + DHA	100	1.3	—	—	Olive oil
Risk & Prevention, 2013[60]	64	4,818 (38.5)	10577 (84.6)	10580 (84.5)	7,494 (60)	EPA + DHA	6244	0.87	150	131.8	Olive oil
REDUCE-IT, 2018[4]	64	2,357 (28.8)	5,785 (70.7)	—	4,787 (58.5)	EPA	4089	4.0	216.5	74.0	Mineral oil
SHOT, 1996[61]	59.9	79 (22)	610 (100)	137 (22.5)	—	EPA + DHA	317	3.3	—	—	No treatment
SCIMO, 1999[62]	58.4	44 (19.7)	223 (100)	110 (49.3)	0	EPA + DHA	112	2.0	194.7	158.3	Average European fats
SOFA, 2006[63]	61.5	85 (15.6)	320 (60)	278 (51)	87 (16)	EPA + DHA	273	0.8	—	—	Sunflower oil
SU.FOL.OM3, 2010[64]	60.7	132 (11.7)	951 (84.2)	—	—	EPA + DHA	1248	0.6	106.2	104.3	Gelatin
Shinto et al., 2014[65]	75.5	18 (46.5)	—	—	—	EPA + DHA	13	1.65	—	—	Soybean oil
STRENGTH, 2020[6]	62.5	4,568 (35)	6,035 (46.1)	11420 (87.4)	9,170 (70.2	EPA + DHA	6539	4.0	239.0	75.0	Corn oil
VITAL, 2018[5]	67.1	13,085 (50.6)	0	12884 (49.8)	3,459 (13.7)	EPA + DHA	12933	0.84	—	—	Vitamin D3

* Supplements include Vitamin C (500 mg/d), Vitamin E (400IU/d), beta-carotene (15 mg/d), zinc oxide (80 mg/d) and cupric oxide (2 mg/d).



Effect of omega-3 fatty acid on non-fatal myocardial infarction.

Interpretation

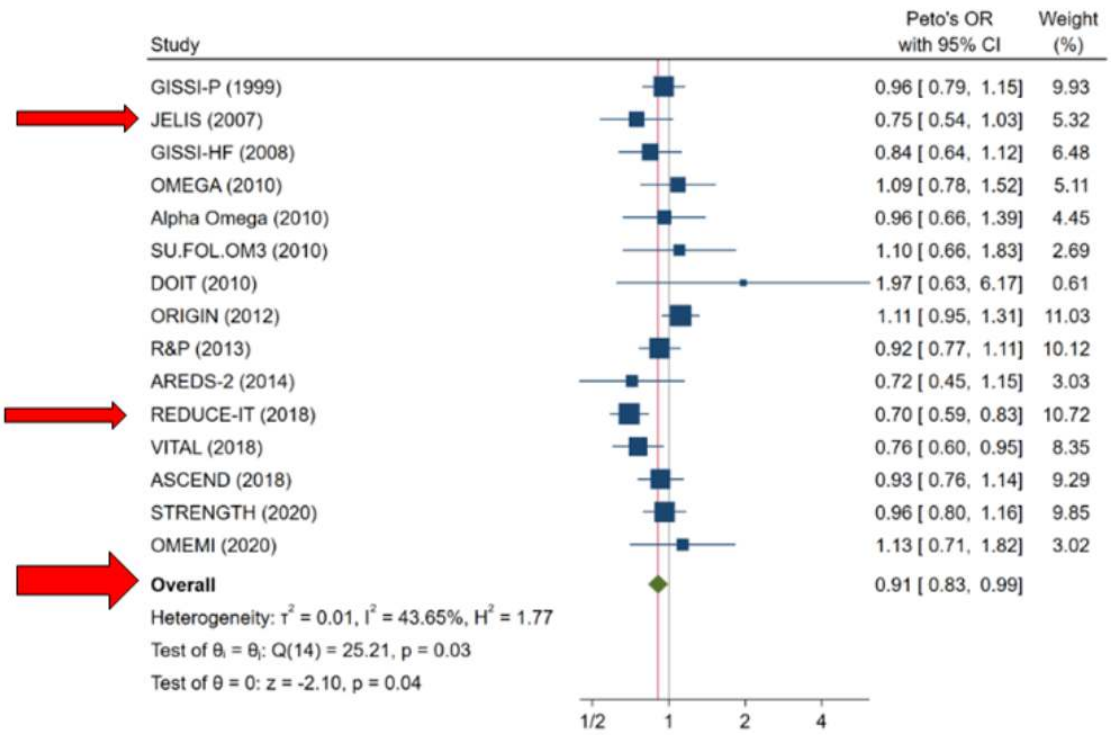
Omega-3 FAs reduced cardiovascular mortality and improved cardiovascular outcomes. The cardiovascular risk reduction was more prominent with EPA monotherapy than with EPA+DHA.

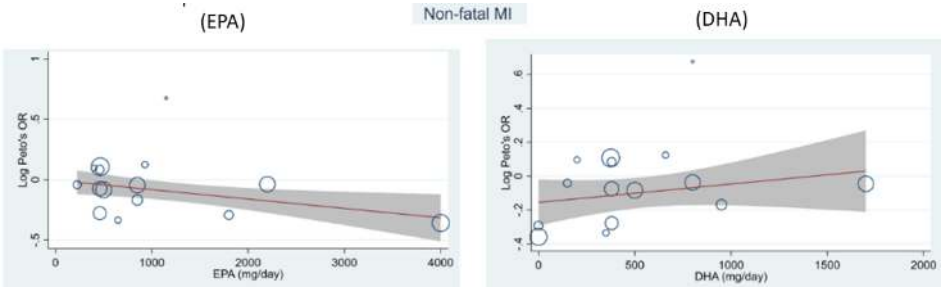
Junta de Castilla y León

Sacyl

Complejo Asistencial Universitario de León

Dose-Dependent Risk Reduction for Myocardial Infarction with Eicosapentaenoic Acid: a Meta-analysis and Meta-regression





Cardiovascular Drugs and Therapy (2021) 35:1079–1081

Junta de Castilla y León

Sacyl

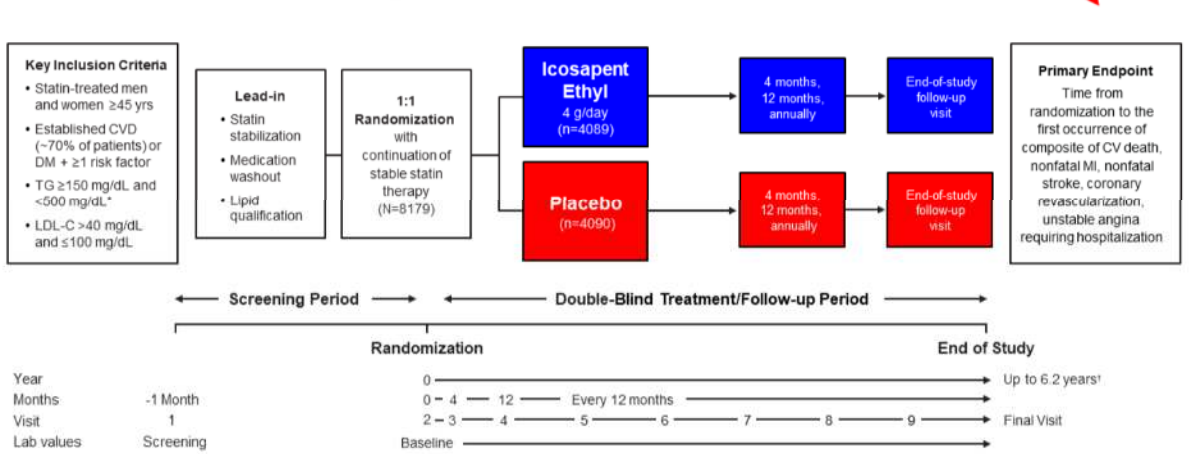
Complejo Asistencial Universitario de León

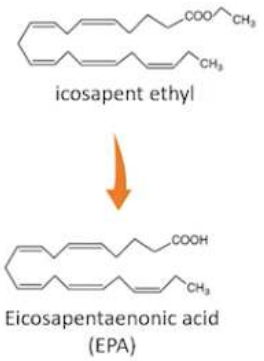
REDUCE-IT Design

REDUCE IT
8179 pacientes
PS (71%) ó DM + ≥ 1 FRCV
Mediana TG 216 mg/dL

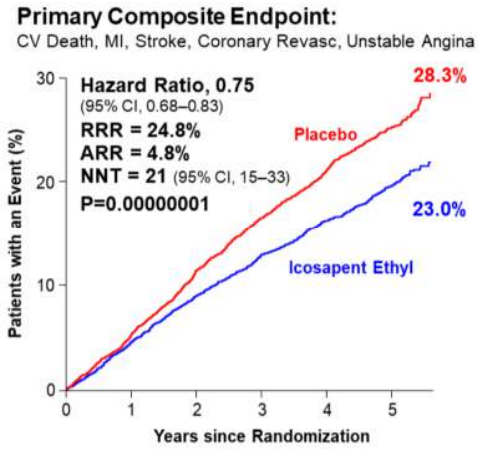
C- LDL 40-100 mg/dL
4gr. EPA VS Placebo
Seguimiento 4.9 años

↓ Triglicéridos 17%

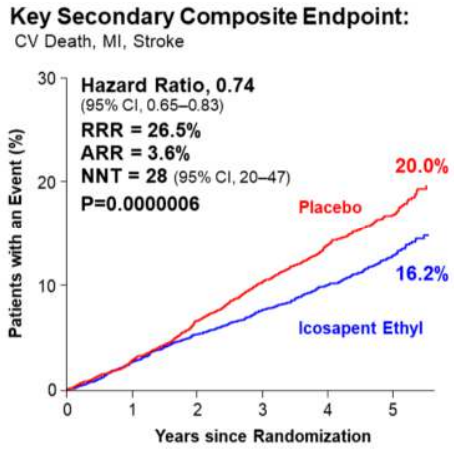


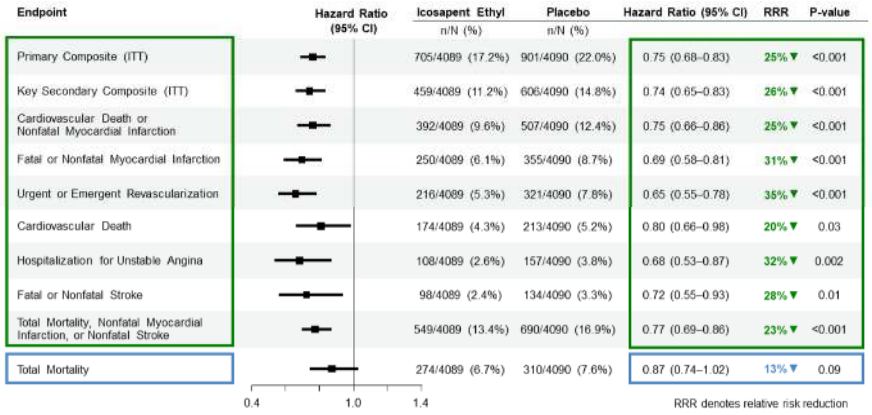


MACE 5 p.



MACE 3 p.



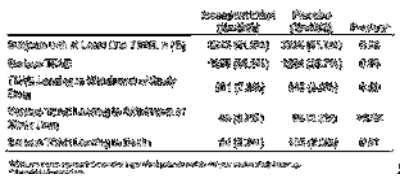


Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular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

0.4 1.0 1.4

RRR denotes relative risk reduction

↓ TG 17% Biomarker	Visit	Icosapent Ethyl (N=4089) Median Observed Value	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value[1]
Triglycerides (mg/dL)	Baseline	216.5			
	Month 4	177.0	-37.5	-18.6	<0.001
	Year 1	175.0	-39.0	-18.3	<0.001
	Year 2	173.0	-38.5	-18.9	<0.001
	Year 3	167.0	-44.0	-21.7	<0.001
	Year 4	163.0	-42.5	-21.7	<0.001
	Year 5	158.0	-38.0	-20.0	<0.001
	Last Visit	170.0	-45.0	-21.6	<0.001



N Engl J Med. 2019; 380:11-22.

Junta de Castilla y León

Sacyl

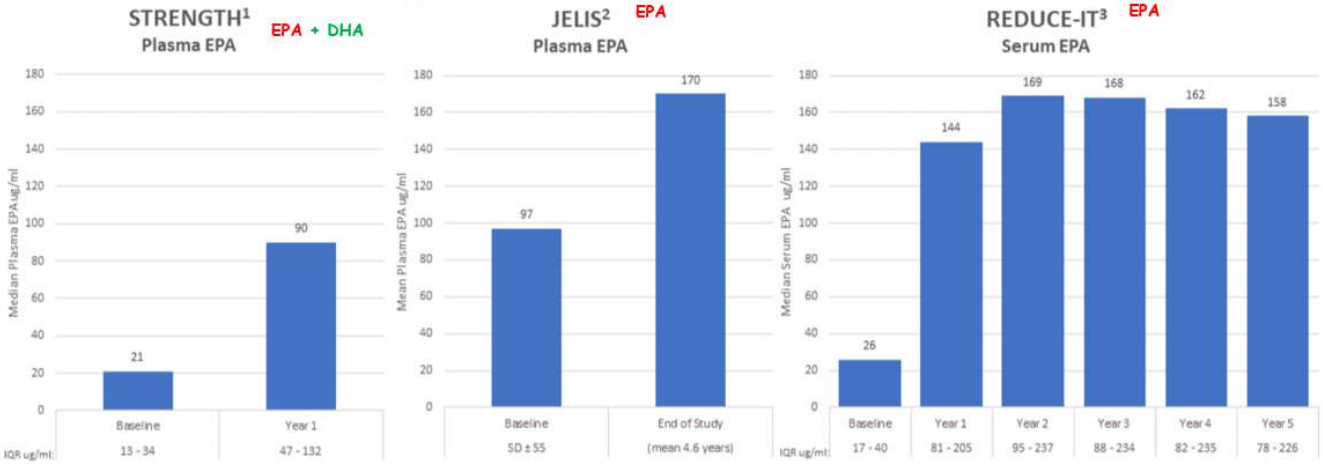
Complejo Asistencial Universitario de León

Table Recent Cardiovascular Outcome Trials with Omega-3 Fatty Acids

	JELIS (18,645)	REDUCE-IT (8179)	STRENGTH (13,078)
Population*	Hypercholesterolemic	High cardiovascular risk, Elevated TG	High cardiovascular risk, Elevated TG, low HDL
Formulation	IPE (1.8 g/d EPA)	IPE (4 g/d EPA)	EPA/DHA carboxylic acids (4 g/d)
Baseline median TG (mg/dL)	153	216	240
Baseline EPA (μg/mL)	97	26.1	21.0
Achieved EPA (μg/mL)	169	144	89.6
Increase in achieved EPA levels (%)	70	394	269
TG lowering (%)	9	17	19
Primary endpoint	Major coronary events	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina	Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina
HR, 95% CI of primary endpoint	0.81, 0.69-0.95 (P = .011)	0.75, 0.68-0.83 (P = .00000001)	0.99, 0.90-1.09 (P = .84)

CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; HR = hazard ratio; IPE = icosapent ethyl; MI = myocardial infarction; TG = triglyceride.
*Statin use was 100%.

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



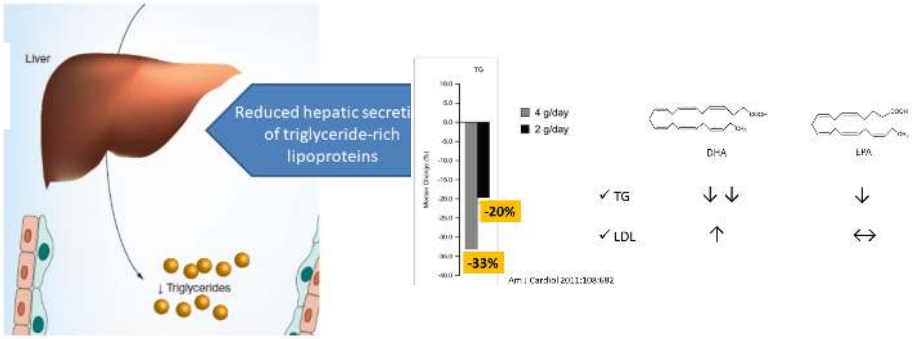
Drug:	850 mg mixed omega-3 carboxylic acid / 1g capsule	>980 mg EPA ethyl ester / 1g capsule	1g icosapent ethyl (EPA ethyl ester) / 1g capsule
Dose:	4 g/d	1.8 g/d	4 g/d
Population:	International	Japanese	International

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.

Acciones AG PI omega-3 -EPA

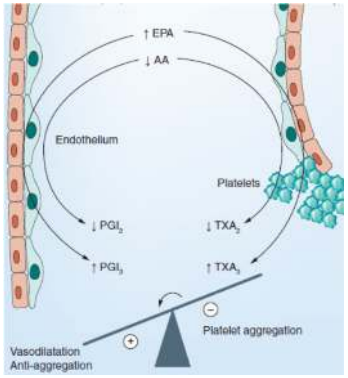
↓TG

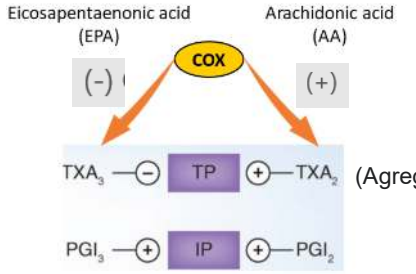


- Reducen síntesis hepática de triglicéridos y VLDL.
- (-) acil-CoA:1,2-diaglicerol aciltransferasa que interviene en la síntesis de TG.
- Reducen síntesis y secreción de QM.
- Acelera el aclaramiento postpandrial de los TG.

	Hazard Ratio (95% CI):
Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL	0.99 (0.84–1.16)

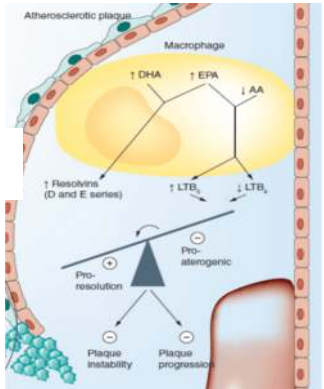
Anti-Trombótico

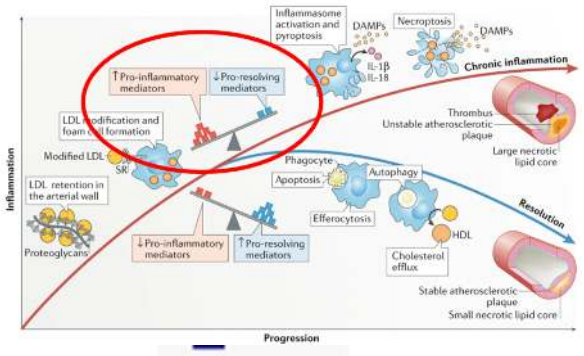


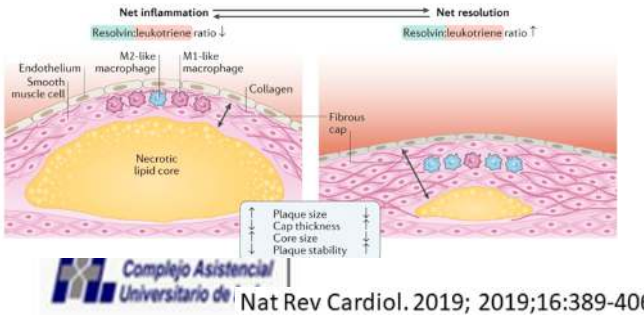


(Agregante plaquetario y VC).

Anti- Inflamatorio







Complejo Asistencial Universitario de

Nat Rev Cardiol. 2019; 2019;16:389-406

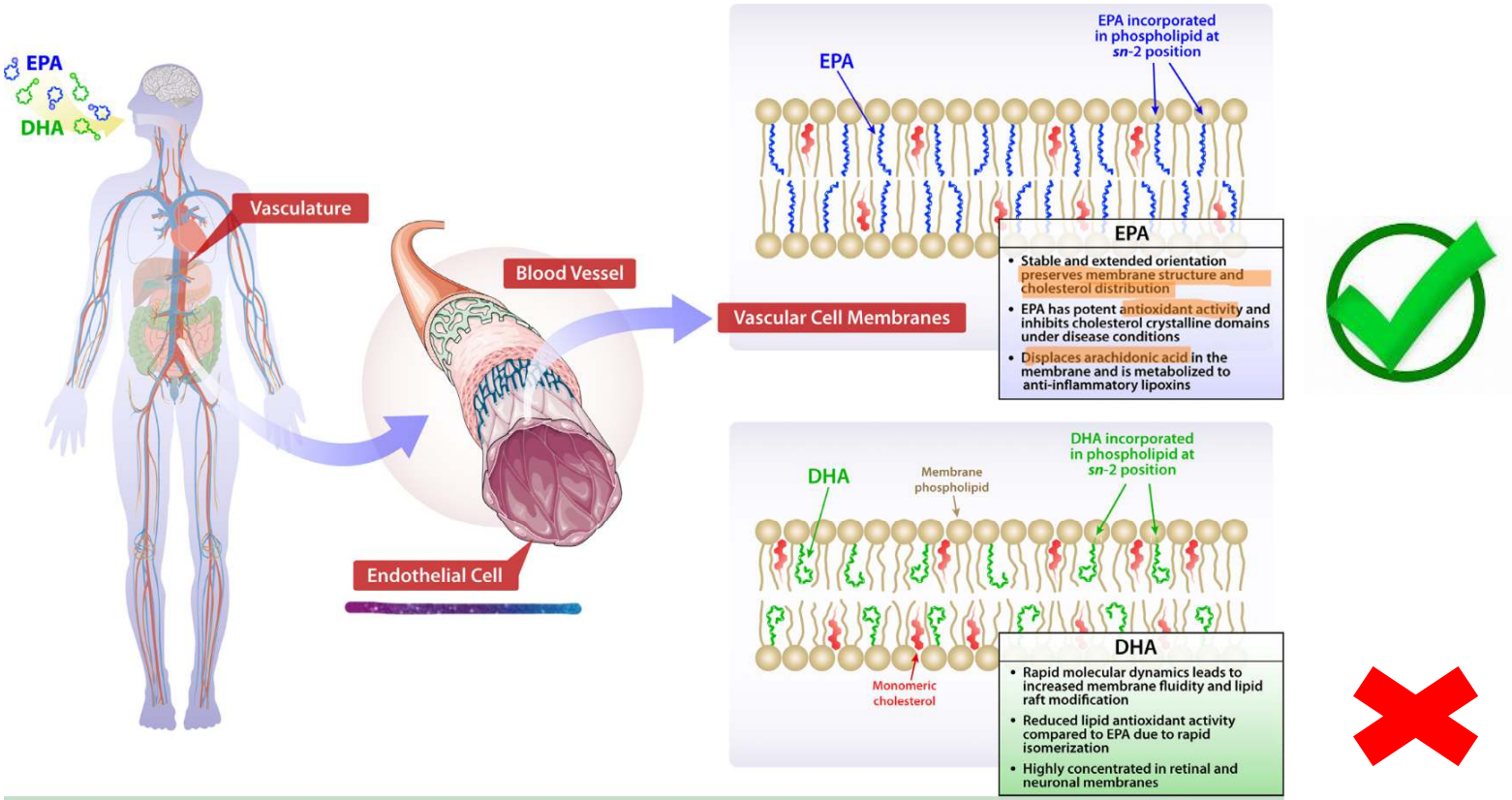
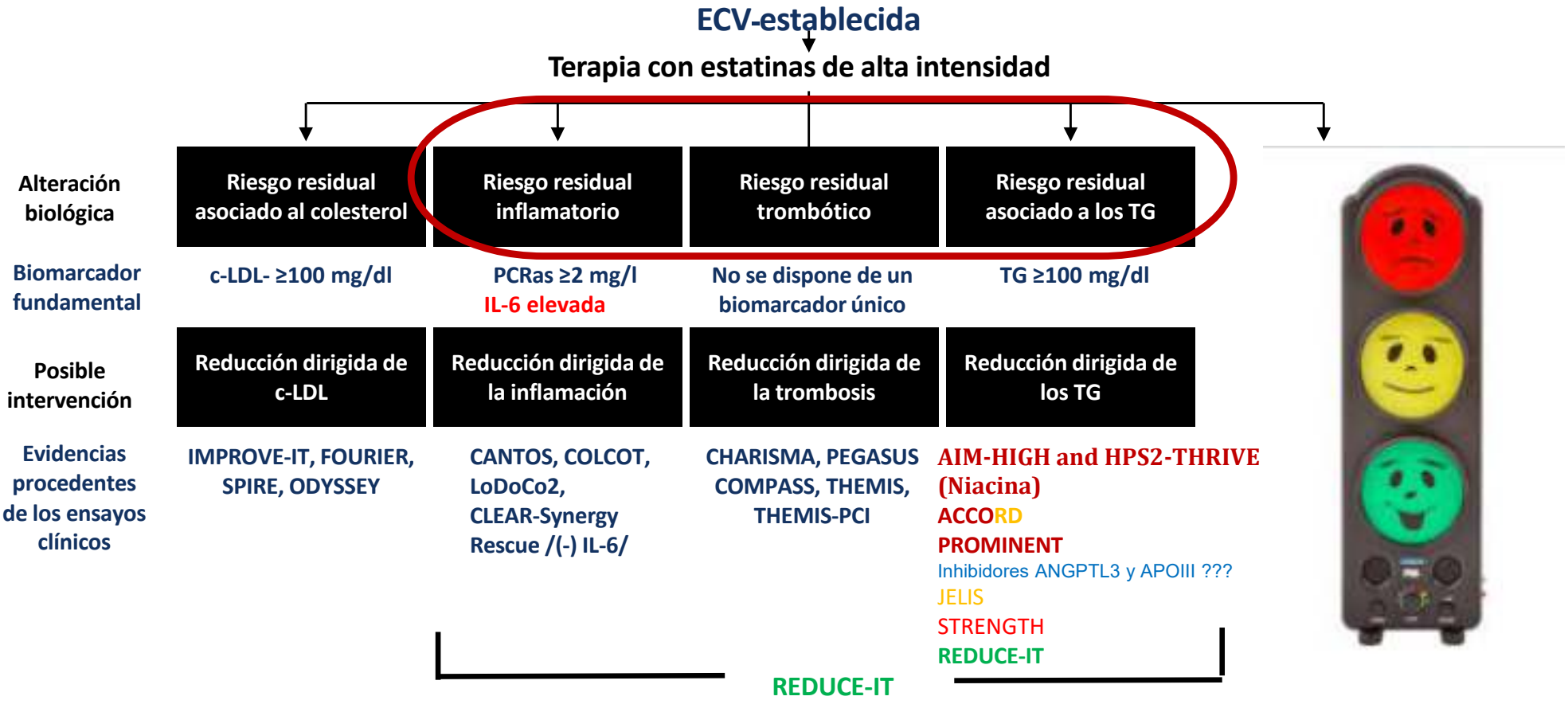


Figure 1 Schematic illustration of the proposed location and contrasting effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on membrane structure, lipid oxidation, and tissue distribution. Eicosapentaenoic acid and DHA have distinct effects on membrane structure and dynamics due to differences in their hydrocarbon length and number of double bonds. The greater hydrocarbon length and number of double bonds for DHA leads to more rapid isomerization and conformational changes that result in increased membrane fluidity and promotion of cholesterol domains. Eicosapentaenoic acid has a more stable and extended structure that contributes to membrane stability as well as inhibition of lipid oxidation and cholesterol domain formation under disease-like conditions.[20]

Riesgo CV residual es la suma de varios factores



ECVA, enfermedad cardiovascular aterosclerótica; CV, cardiovascular; Lp (a), lipoproteína (a); c-LDL, colesterol unido a lipoproteínas de baja densidad; LoDoCo2, colchicina en dosis bajas; TG, triglicéridos.

Mason RP et al. *Arterioscler Thromb Vasc Biol*. 2020:40(5):1135-1147. + CTN

Clínica e Investigación en Arteriosclerosis xxx (xxxx) xxx–xxx 04/2023

Sociedad Española de Arteriosclerosis

CLÍNICA E INVESTIGACIÓN EN ARTERIOSCLEROSIS

www.elsevier.es/arterio

DOCUMENTO DE CONSENSO

Documento de consenso para la determinación e informe del perfil lipídico en laboratorios clínicos españoles ¿Qué parámetros debe incluir un perfil lipídico básico?☆

	RCV muy alto	RCV alto
	LDL < 55 mg/dl	LDL < 70 mg/dl
LDL-C	**Very-high risk in primary or secondary prevention:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required. **High risk:** A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL).	
Non-HDL-C	< 85 mg/dl	< 100 mg/dl
ApoB	< 65 mg/dl	< 80 mg/dl
Colesterol remanente	**< 30 mg/dL**	

OBJETIVO compuesto: c-LDL y CR → apoB

Colesterol remanente: QMr+VLDLr+IDL : **CT** – cLDL – **CHDL**

Apo B-100 LP: VLDL, IDL, LDL y Lp(a)-Apo(a).

Tríada lipídica aterogénica:	Si: TG > 150 mg/dL y c-HDL < 30 mg/dL c-LDL/Apo B < 1,3 o TG/c-HDL > 2

Tabla 2 Valores lipídicos deseables adultos según las Sociedades Europeas de cardiología, arteriosclerosis y medicina de laboratorio[17,18,3,6]

Parámetro	Valor deseable adultos
Colesterol total	< 200 mg/dL (5,17 mmol/L)
Colesterol-HDL	> 50 mg/dL mujeres (1,29 mmol/L) > 40 mg/dL hombres (1,03 mmol/L)
Colesterol no-HDL	Valores recomendados según el RCV • Prevención secundaria y RCV muy alto < 85 mg/dL (< 2,2 mmol/L) • RCV alto < 100 mg/dL (< 2,6 mmol/L • RCV moderado < 130 mg/dL (< 3,.4 mmol/L)
Colesterol LDL	Valores recomendados según RCV • Prevención secundaria y RCV muy alto < 55 mg/dL (< 1,4 mmol/L) • RCV alto < 70 mg/dL (< 1,8 mmol/L • RCV moderado < 100 mg/dL (< 2,6 mmol/L) • RCV bajo < 116 mg/dL (< 3 mmol/L)
Triglicéridos	TG < 150 mg/dL en ayunas (<1,69 mmol/L) (TG < 175 mg/dL no en ayunas) (<1,97 mmol/L)
Colesterol de partículas residuales	< 30 mg/dl (0,78 mmol/L) en ayunas < 30 mg/dl (0,91 mmol/L) no en ayunas
Apolipoproteína B	Valores recomendados según RCV • Prevención secundaria y RCV muy alto < 65 mg/dL (1,27 µmol/L) • RCV alto < 80 mg/dL (1,56 µmol/L) • RCV moderado < 100 mg/dL (1,95 µmol/L)
Lp(a)	< 50 mg/dL (< 105 nmol/L)

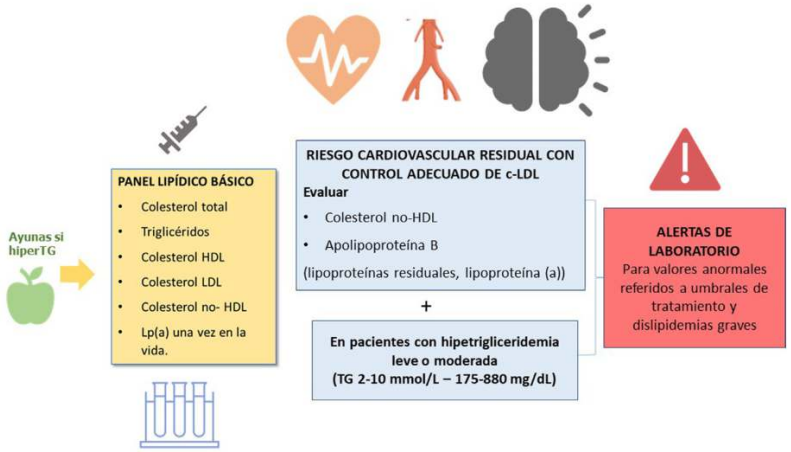
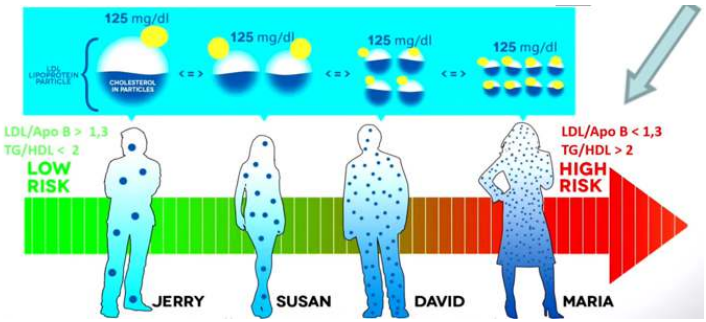


Figura 1 Recomendaciones básicas para el informe de perfil lipídico en laboratorios clínicos españoles.

Junta de Castilla y León · Sacyl · Complejo Asistencial Universitario de León



Recommendations for drug treatments of patients with hypertriglyceridaemia.

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[534–536]	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) may be considered in combination with a statin.[84]	IIb	B

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acid.

ACUERDOS DE LA COMISION INTERMINISTERIAL DE PRECIOS DE LOS MEDICAMENTOS

Sesión 230 de 15 de diciembre de 2022

MINISTERIO DE SANIDAD

SECRETARIA DE ESTADO DE SANIDAD

Ácido eicosapentanóico (EPA)

MEDICAMENTO	FORMATO	CN	Criterios para la financiación
VAZKEPA 998 MG CAPSULAS BLANDAS	120 cápsulas	731254	d)

Principio activo: C10AX06 – Triglicéridos omega-3, incluidos otros ésteres y ácidos

Indicación terapéutica autorizada:

Vazkepa está indicado para reducir el riesgo de eventos cardiovasculares en pacientes adultos tratados con estatinas con riesgo cardiovascular alto con triglicéridos altos (≥ 150 mg/dl [≥ 1,7 mmol/l]) y

- una enfermedad cardiovascular diagnosticada, o
- diabetes y, al menos, otro factor de riesgo cardiovascular.