

# Els triglicèrids com a marcador de risc vascular. Què fem?

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# Conflictes d'interès



## **Consultor/assessor:**

Administración Nacional de Educación Pública (ANEP), Agència per a la Qualitat del Sistema Universitari (AQU) de Catalunya i Agència Valenciana d'Avaluació i Prospectiva (AVAP)

## **Ponent:**

AMARIN PHARMA, AMGEN, ASTRA ZENECA, DAIICHI-SANKYO, ESTEVE, FERRER, MERCK SHARP & DOHME, MYLAN (VIATRIS), ROVI, SANOFI i SERVIER

**No hi ha cap conflicte d'interès per aquesta presentació**

# Institut Nacional Estadística (INE)

## Defuncions segons causa de mort, any 2020

### Defunciones por capítulos de la CIE-10. Año 2020

Valores absolutos y porcentajes

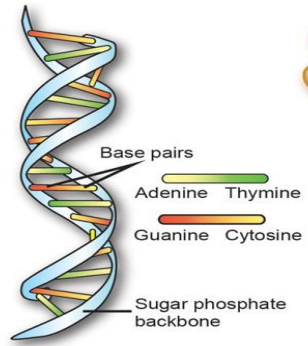
Capítulos de la CIE-10	Defunciones	%
Total Defunciones	493.776	100,0
Enfermedades del sistema circulatorio	119.853	24,3
Tumores	112.741	22,8
Enfermedades infecciosas y parasitarias(1)	80.796	16,4
Enfermedades del sistema respiratorio	42.423	8,6
Enfermedades del sistema nervioso y de los órganos de los sentidos	27.508	5,6
Trastornos mentales y del comportamiento	21.697	4,4
Enfermedades del sistema digestivo	21.565	4,4
Causas externas de mortalidad	16.078	3,3
Enfermedades del sistema genitourinario	15.810	3,2
Enfermedades endocrinas, nutricionales y metabólicas	15.290	3,1
Síntomas, signos y hallazgos anormales clínicos y de laboratorio	9.475	1,9
Enfermedades del sistema osteomuscular y del tejido conjuntivo	5.225	1,1
Enfermedades de la sangre y de los órganos hematopoyéticos y ciertos trastornos que afectan al mecanismo de la inmunidad	2.062	0,4
Enfermedades de la piel y del tejido subcutáneo	1.902	0,4
Malformaciones congénitas, deformidades y anomalías cromosómicas	823	0,2
Afecciones originadas en el periodo perinatal	518	0,1
Embarazo, parto y puerperio	10	0,0

↑ 2,8% respecte al 2019

(1) Covid-19 virus identificado y virus no identificado (sospechoso) se incluye en el grupo de las enfermedades infecciosas y parasitarias

Genetic  
Vulnerability

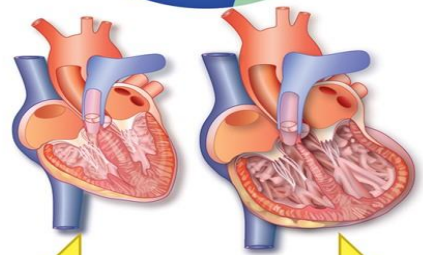
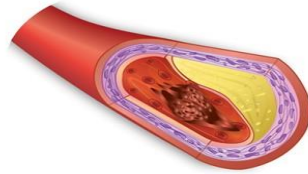
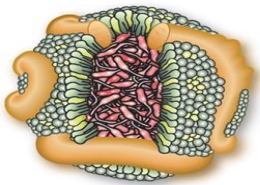
Adaptive  
or  
Maladaptive



Exposures (causal factors or enhancers)  
Magnitude x Duration  
= Cumulative Burden

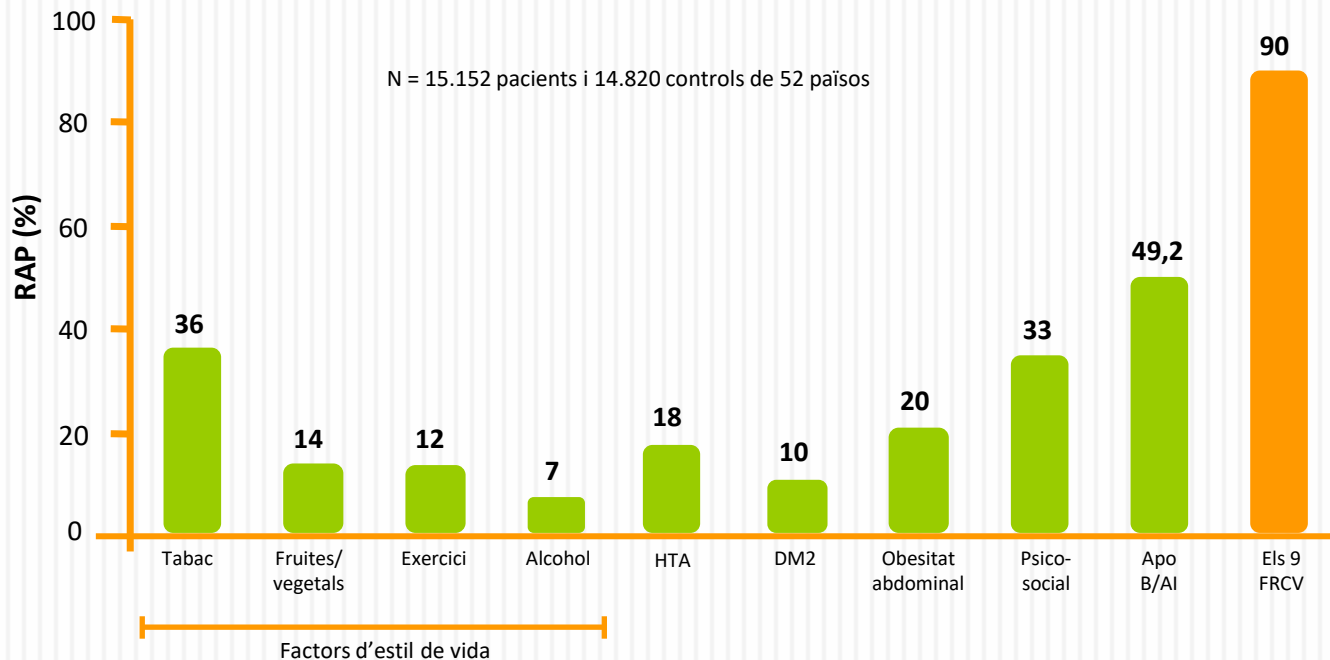
Disease

LDL  
cholesterol



# Efecte dels factors modificables en el IAM

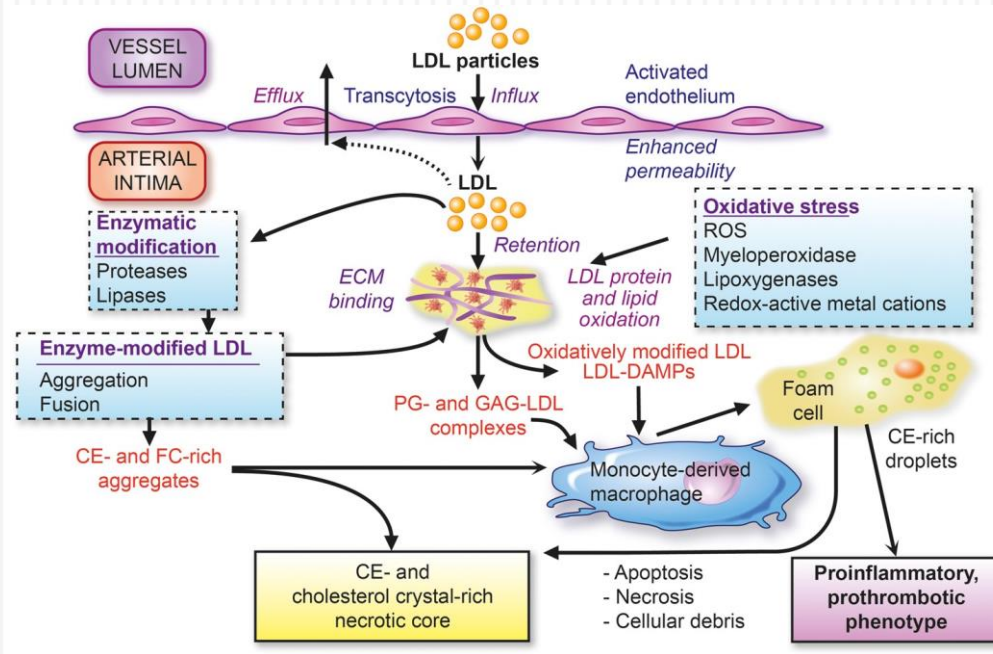
## Estudi INTERHEART



RAP = risc atribuïble a la població, ajustat per tots el FRCV

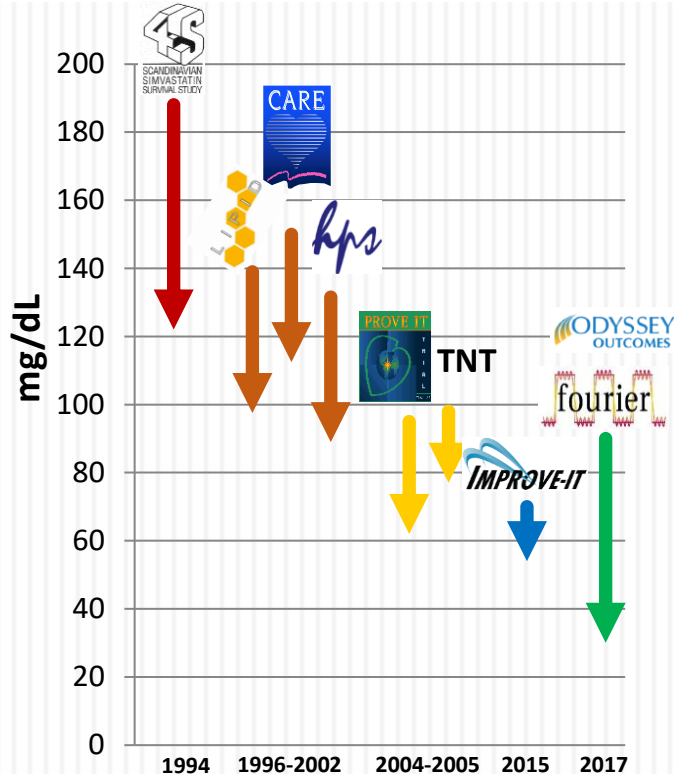
- **Supressió del tabaquisme**
- **Dieta cardiosaludable**
- **Control ponderal**
- **Exercici físic regular**
- **Control de l'estrès**
- **Revisions periòdiques de la pressió arterial, glucèmia i lípids**

# LDL: factor causal de l'arterioesclerosi



# cLDL assolit en els principals estudis aleatoritzats

## Un quart de segle tractant el cLDL



**cLDL alt és dolent**

**cLDL 130-150 mg/dL no és bó**

**cLDL més baix és millor**

**Fins i tot cLDL més baix encara és millor**

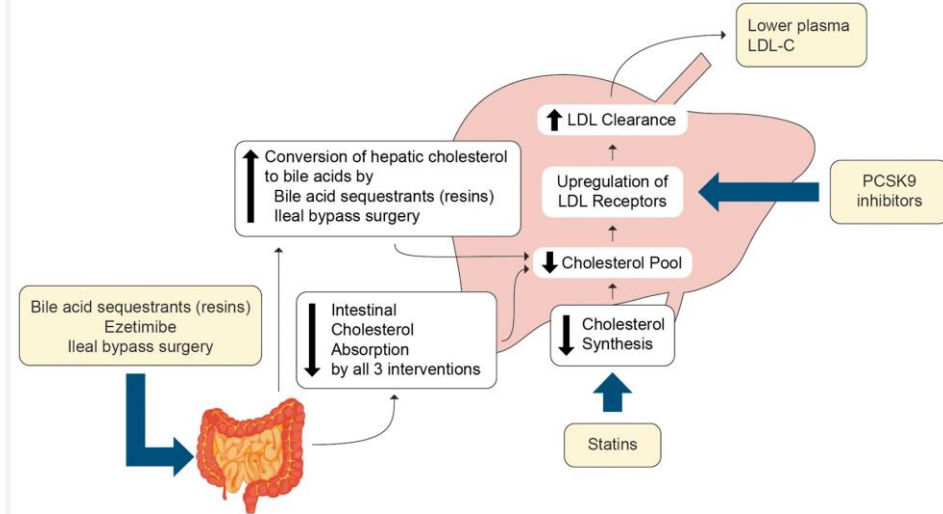
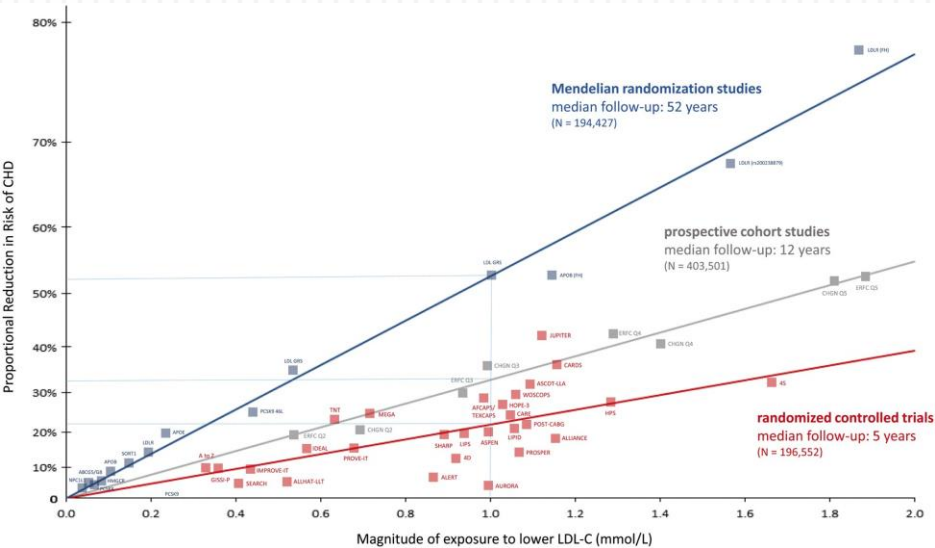
**cLDL el més baix és el millor**

**I COM MÉS AVIAT MILLOR!!!!**

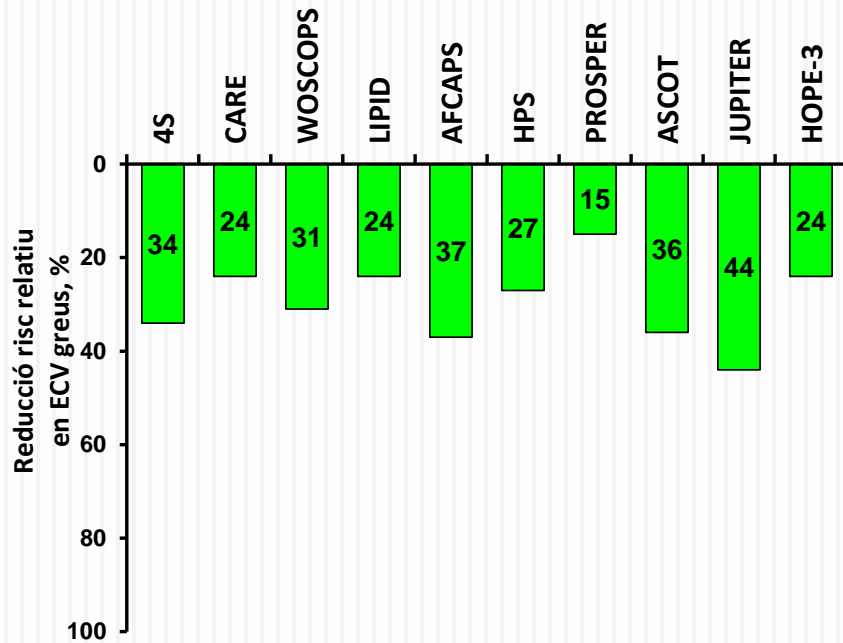


# LDL és causant d'arterioesclerosi

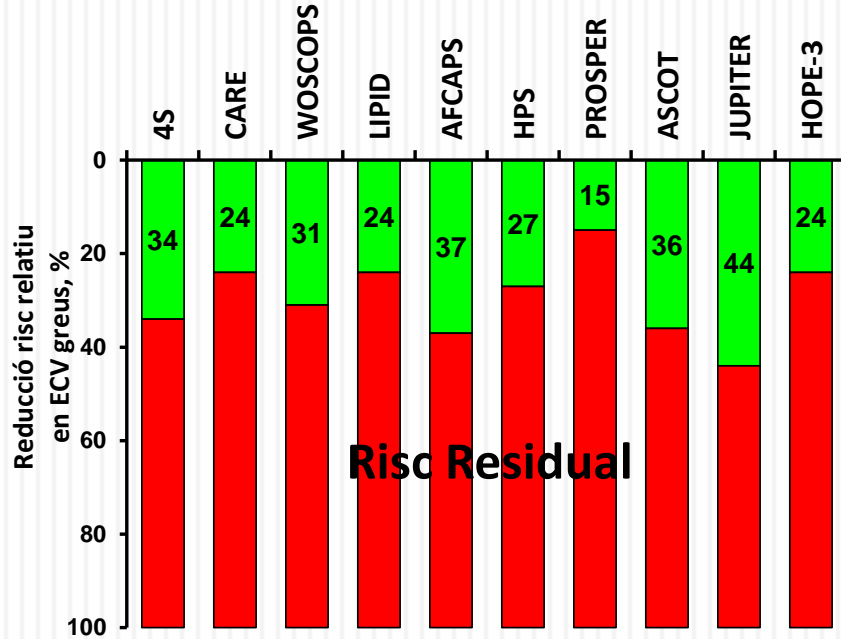
**Metaanàlisi d'estudis d'aleatorització mendeliana, de cohorts prospectives i controlats aleatoritzats estableixen inequívocament que el LDL causa ECV**



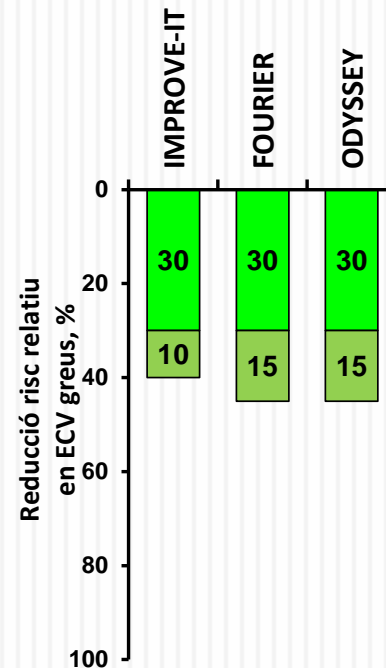
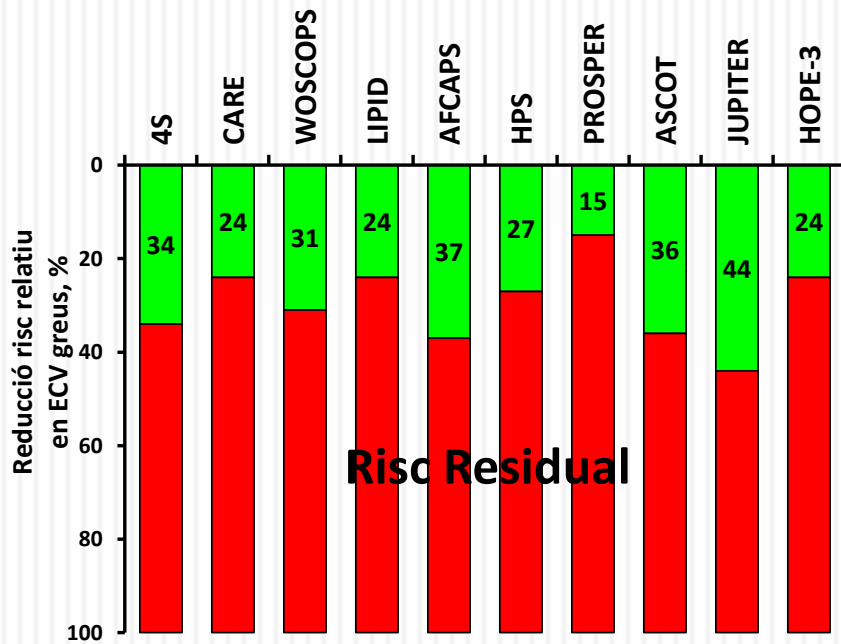
# Tractament hipolipemiànt i risc cardiovascular residual



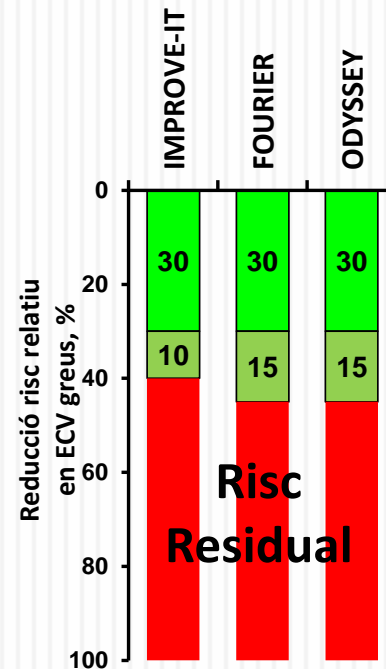
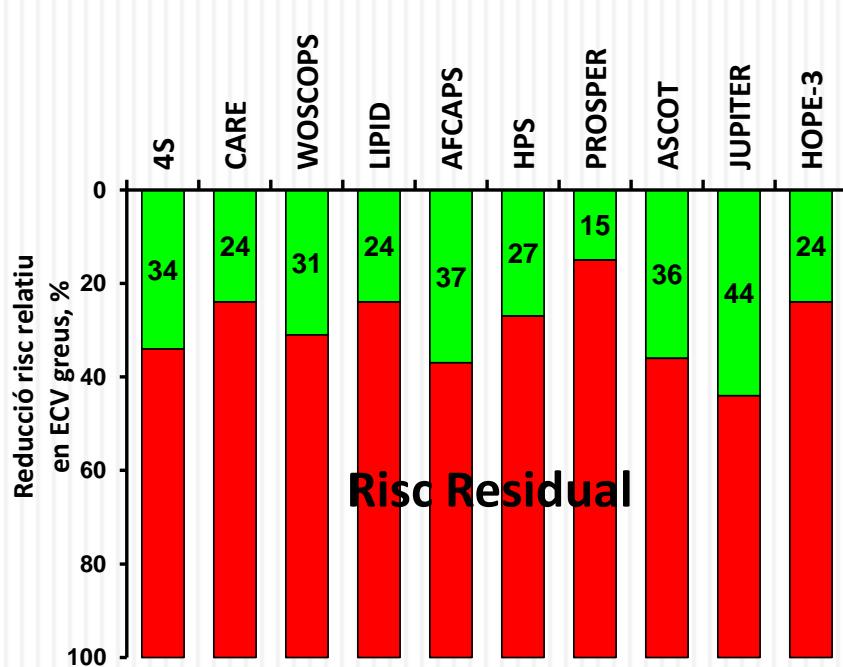
# Tractament hipolipemiànt i risc cardiovascular residual



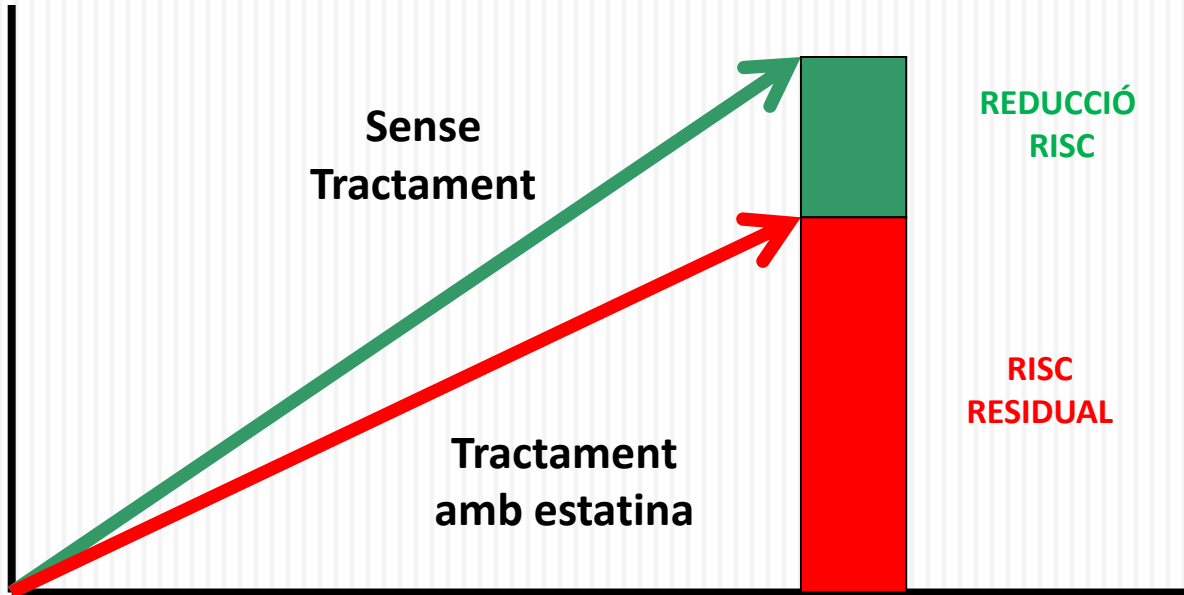
# Tractament hipolipemiànt i risc cardiovascular residual



# Tractament hipolipemiànt i risc cardiovascular residual



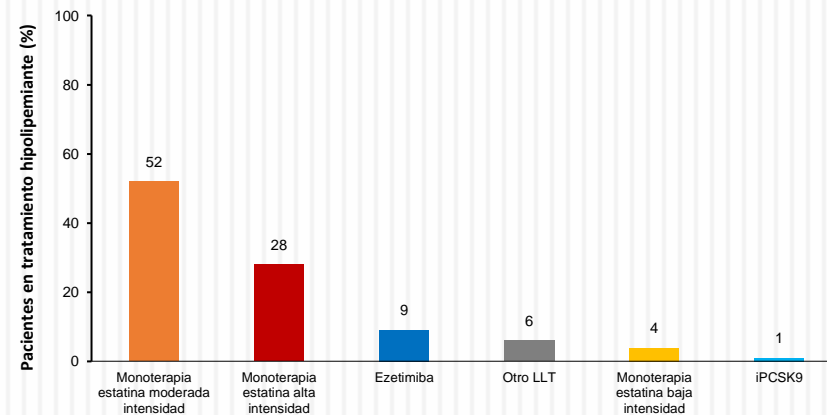
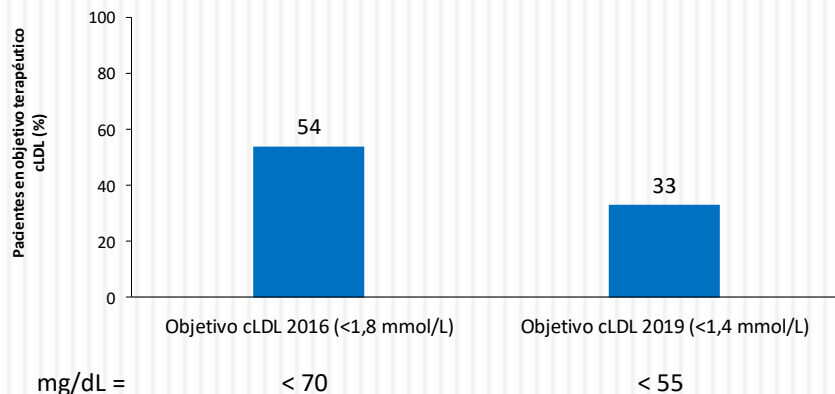
# Risc cardiovascular residual



El RCV residual és aquell que persisteix malgrat els estàndards actuals de tractament i assolir els objectius de cLDL, PA i HbA1c

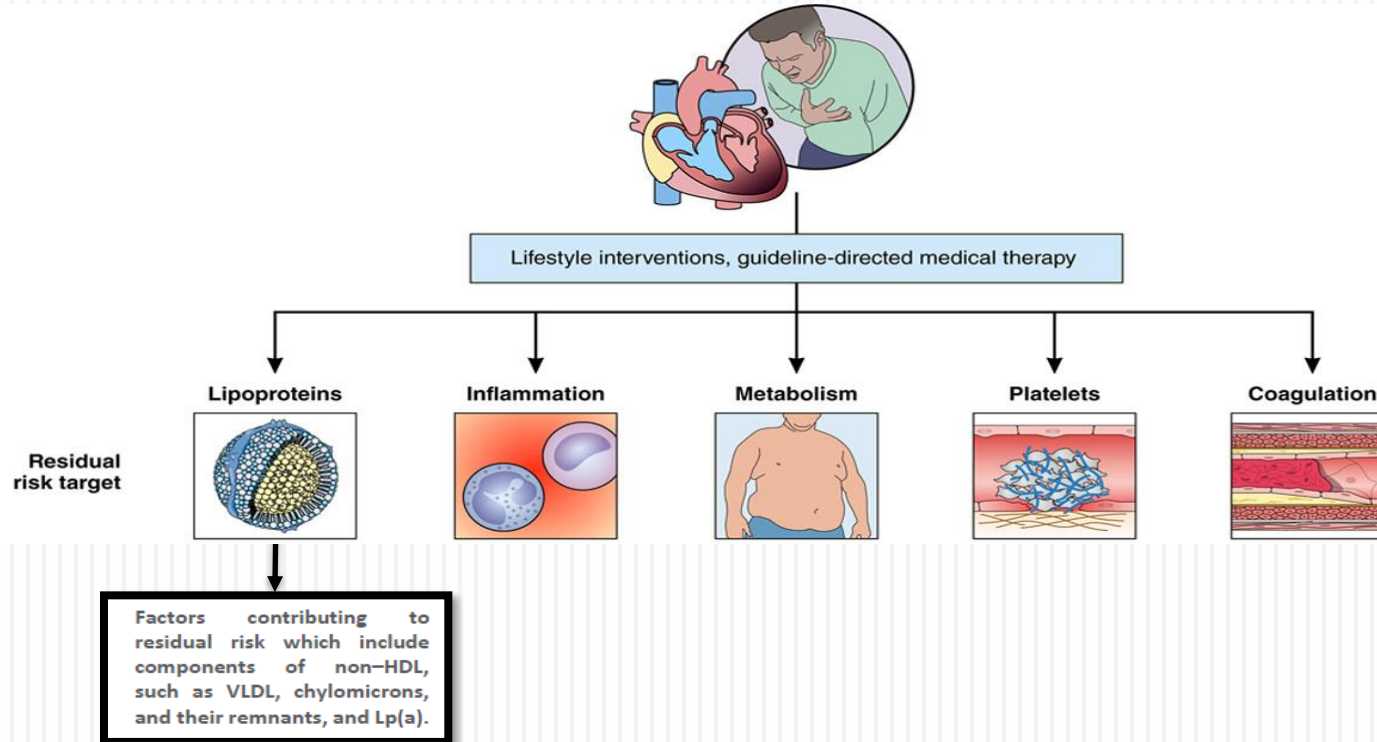
# Estudi DA VINCI

**5.888 pacients: 3.000 en prevenció primària i 2.888 secundària**  
**juny 2017 – novembre 2018**



**El primer enemigo del riesgo residual es no assolir els objectius terapèutics en cLDL**

# Risc cardiovascular residual

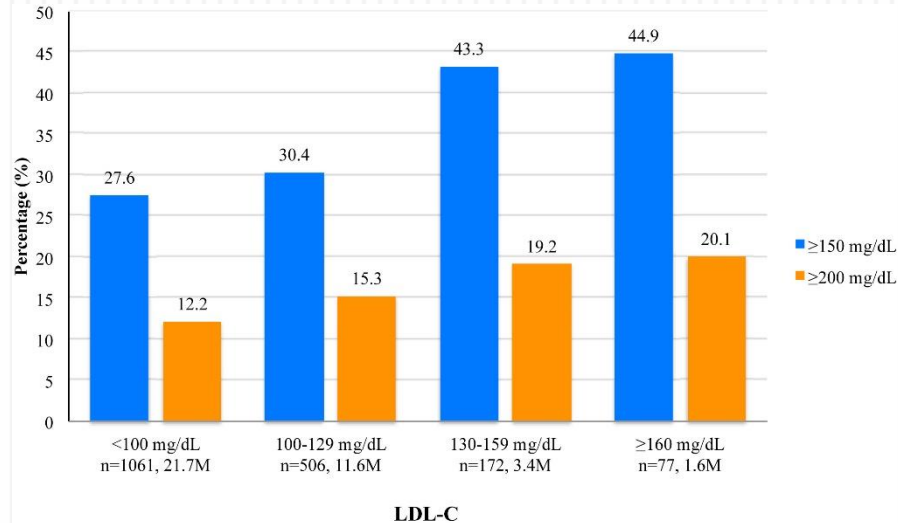




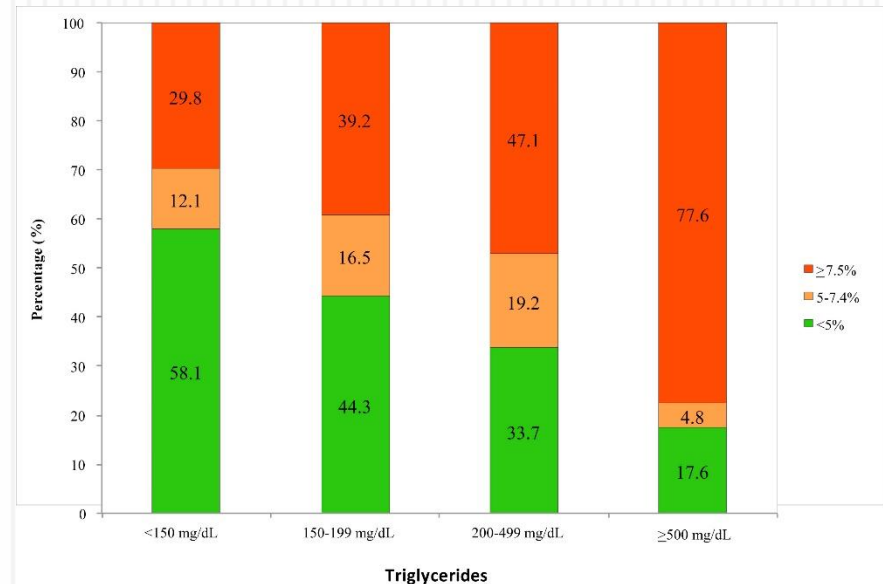
# HTG en adults tractats amb estatina

## National Health and Nutrition Examination Survey

### HTG segons cLDL



### RCV a 10 anys segons TG



# Dislipèmia aterogènica

An iceberg floating in the ocean under a bright sun and blue sky. The visible tip of the iceberg is labeled with 'TG elevats' and 'cHDL baix'. The much larger submerged part of the iceberg is labeled with a list of lipid abnormalities: 'LDL petites i denses', 'VLDL grans', 'HDL petites', 'HDL disfuncionals', 'Augment Apo B', 'Augment part. LDL', 'Augment C no HDL', 'Lipèmia postprandial', and '...'. The background shows a clear blue sky with some clouds and a bright sun with rays.

**TG elevats**

**cHDL baix**

**LDL petites i denses**

**VLDL grans**

**HDL petites**

**HDL disfuncionals**

**Augment Apo B**

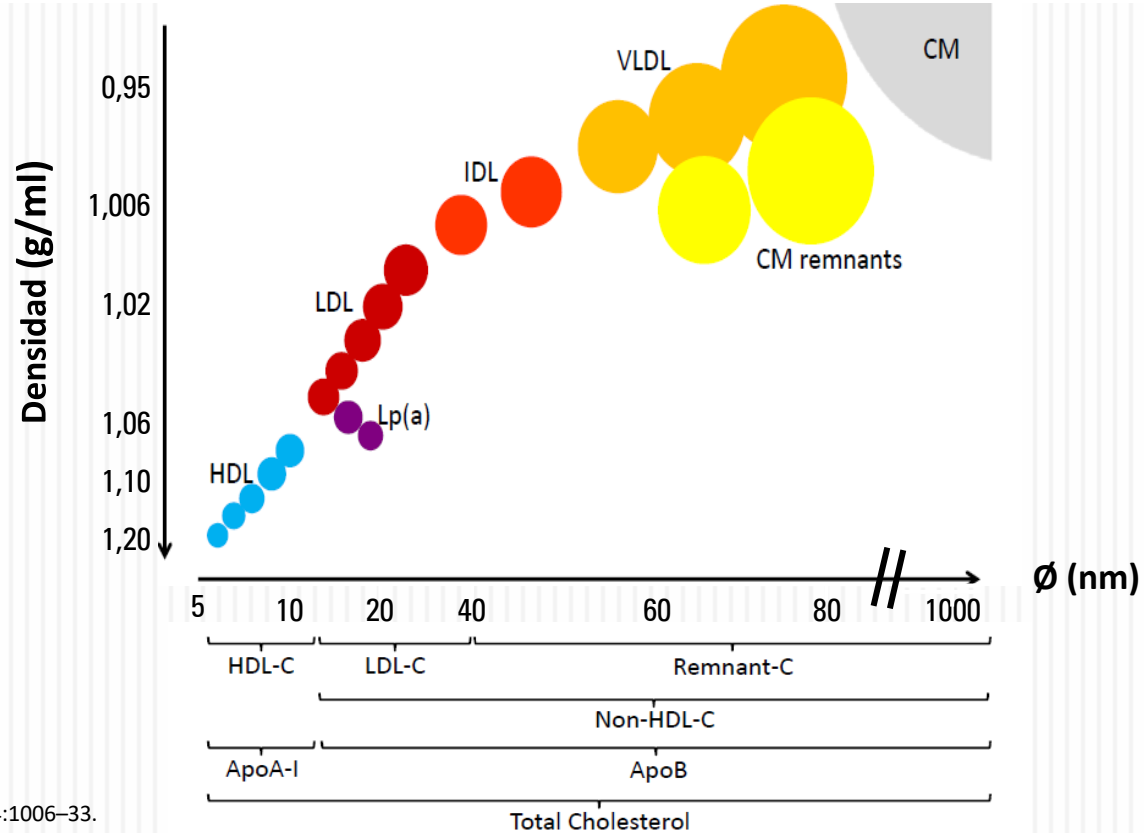
**Augment part. LDL**

**Augment C no HDL**

**Lipèmia postprandial**

**...**

# Partícules lipoproteiques



# Limitacions de la fórmula de Friedewald (cLDL estimat)

- cLDL inclou IDL i Lp(a)
- Assumeix quocient TG/C constant en VLDL (no QM, no rem)
- Equació correcta quan TG < 200 mg/dL
- ↑ Imprecisió quan TG 200 – 400 mg/dL
- Invàlid si TG > 400 mg/dL o HPL tipo III

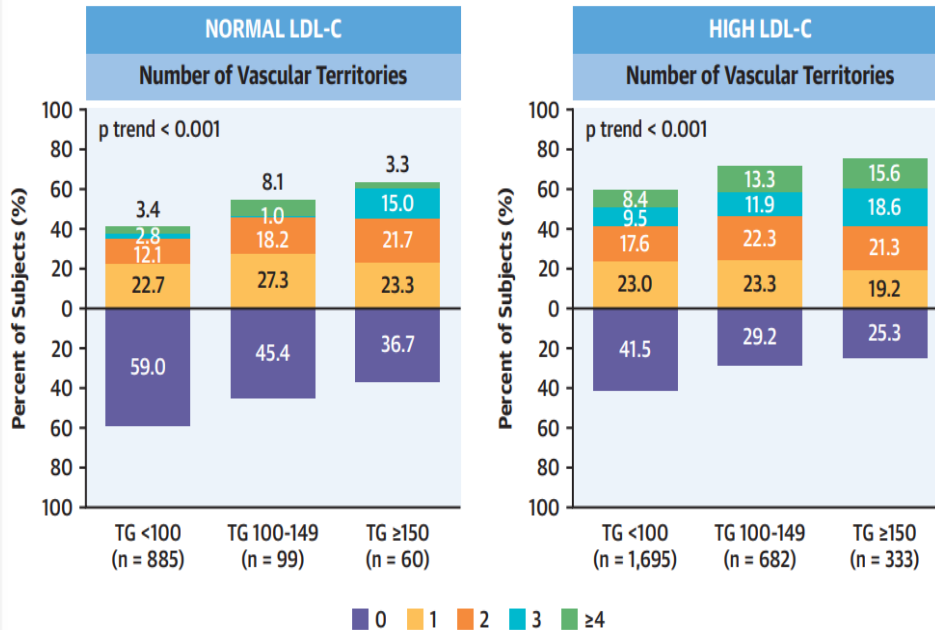


**Rati TG/C en LRT ↑ progressivament en HTG (l'equació sobreestima cVLDL i infraestima cLDL)**

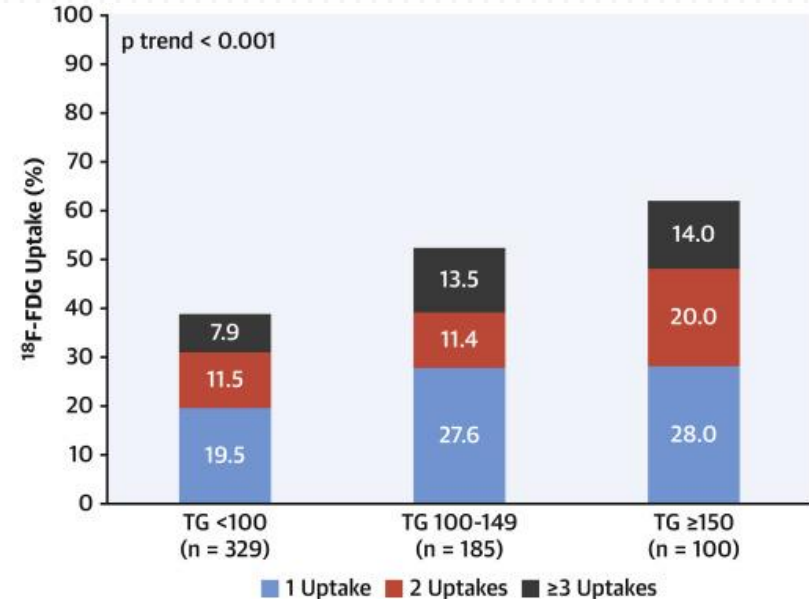
# Triglicèrids i risc cardiovascular residual

## Estudi PESA (subjectes amb RCV baix/moderat)

### Relació entre extensió arterioesclerosi subclínica i TGs

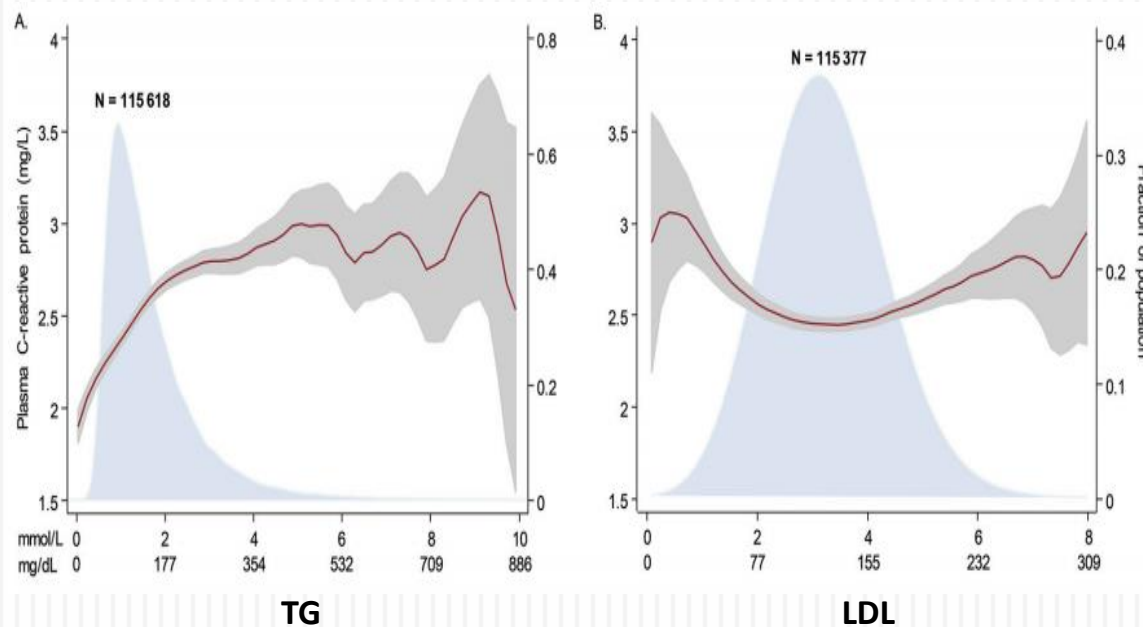


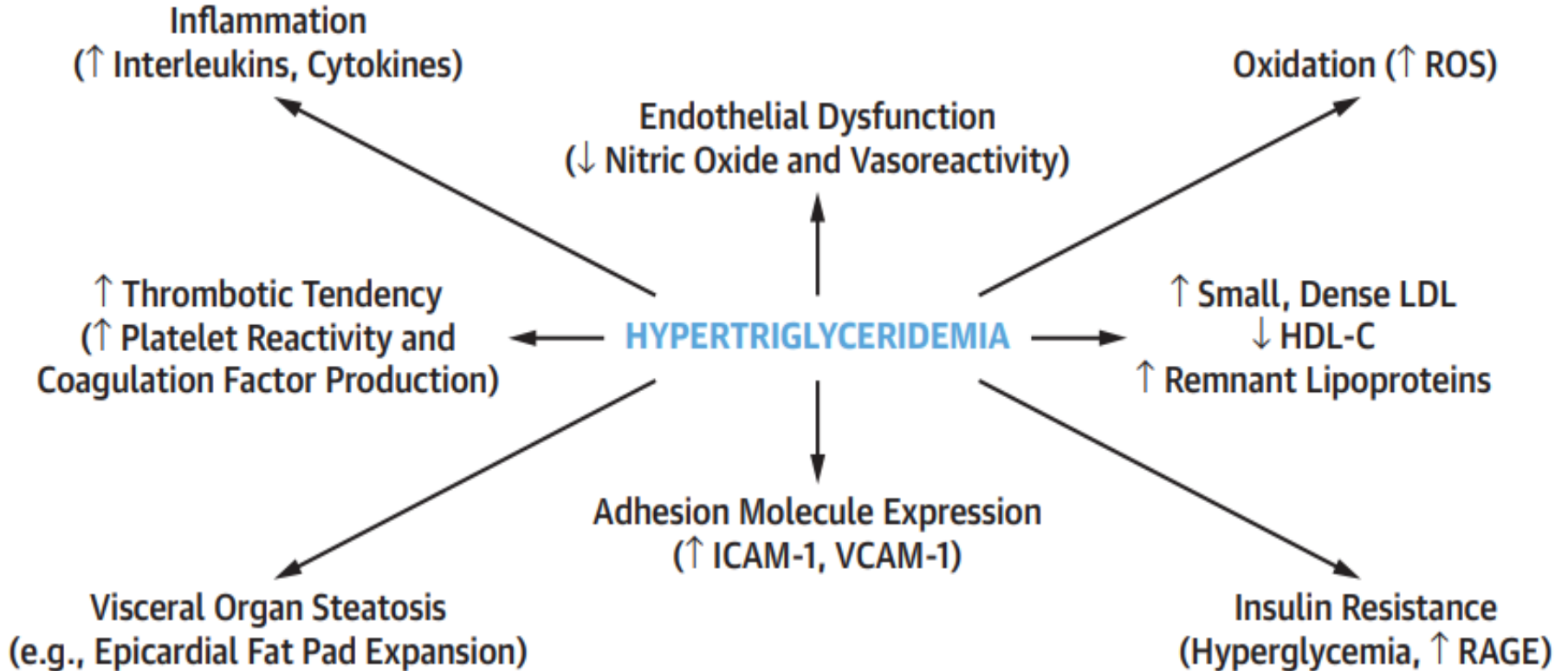
### Relació entre inflamació arterial i TGs



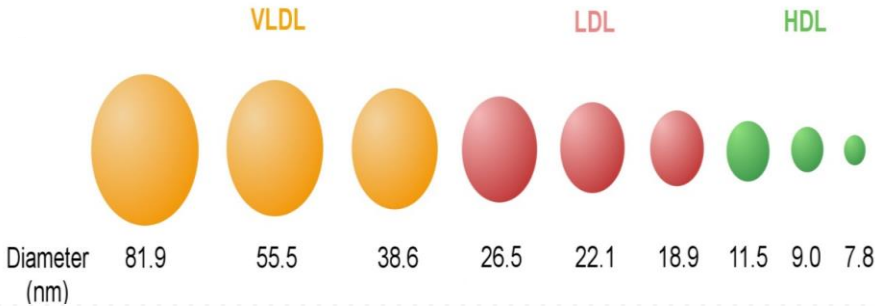
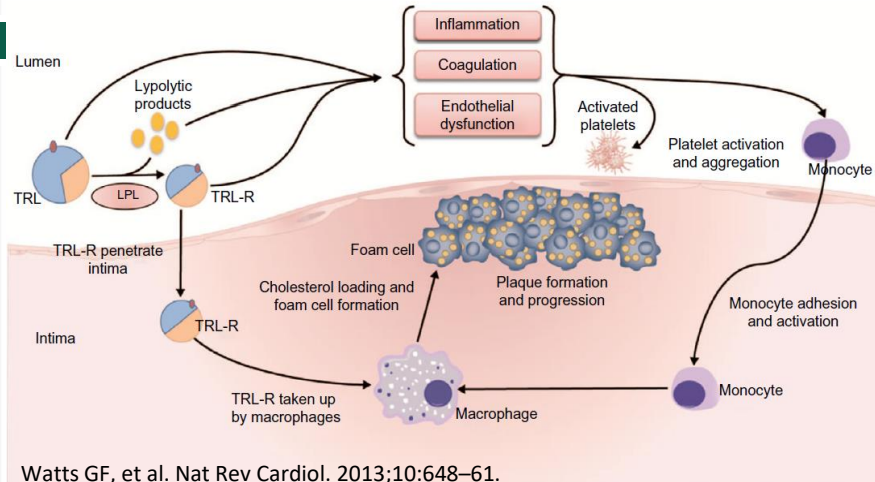
# Les lipoproteïnes riques en TG promouen més inflamació que les LDL

## Copenhagen General Population Study and the Copenhagen City Heart Study

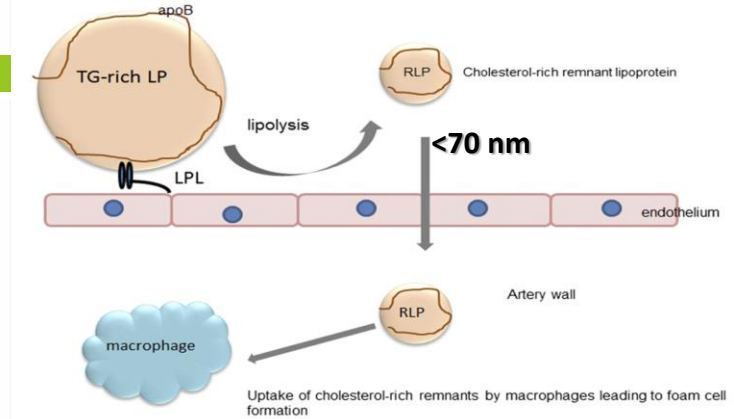




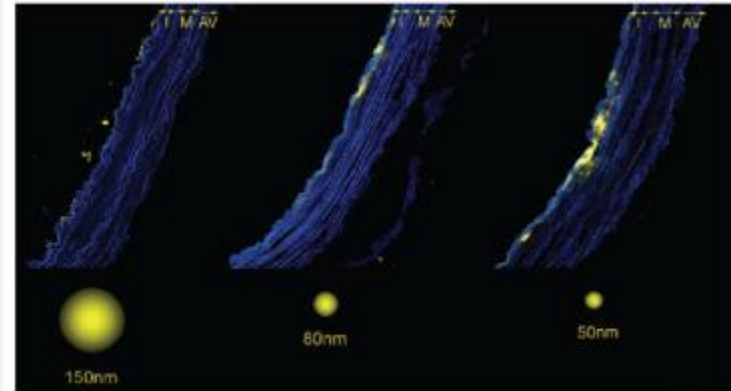
# Lipoproteïnes riques en TG i arterioesclerosi



Mallol R, et al. J Lipid Res. 2015;56:737-46.



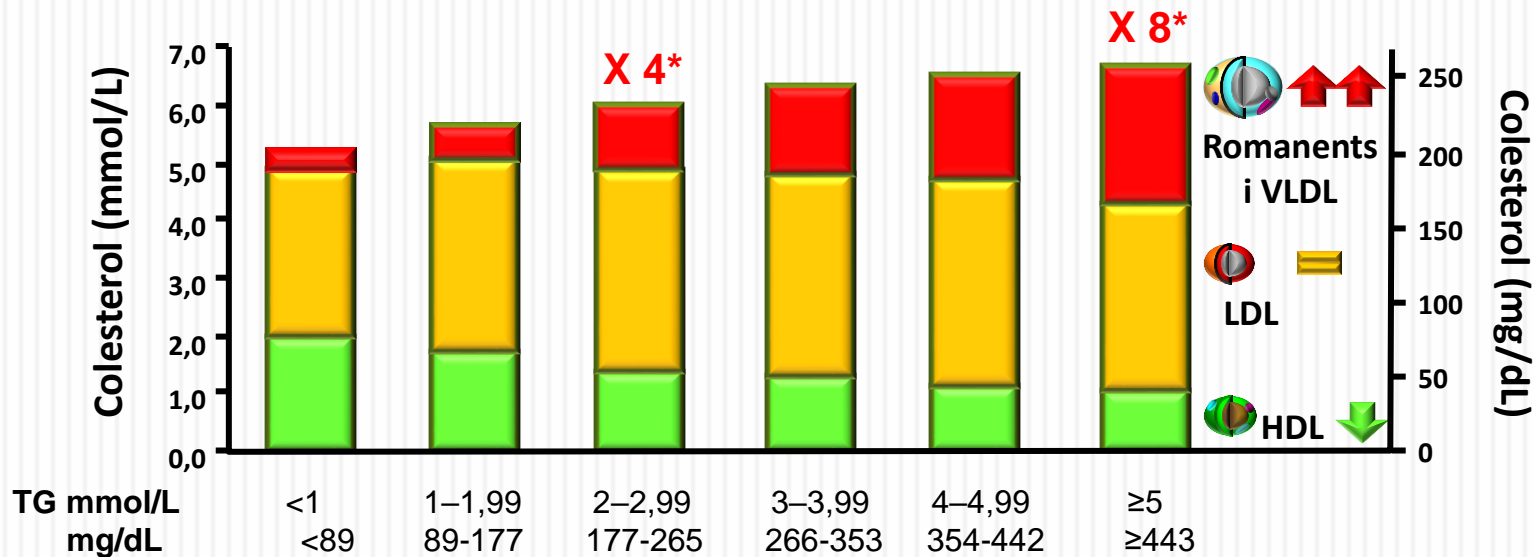
McPherson R. J Am Coll Cardiol. 2013;61:437-9.



Pradhan AD, et al. Am Heart J. 2018;206:80-93.

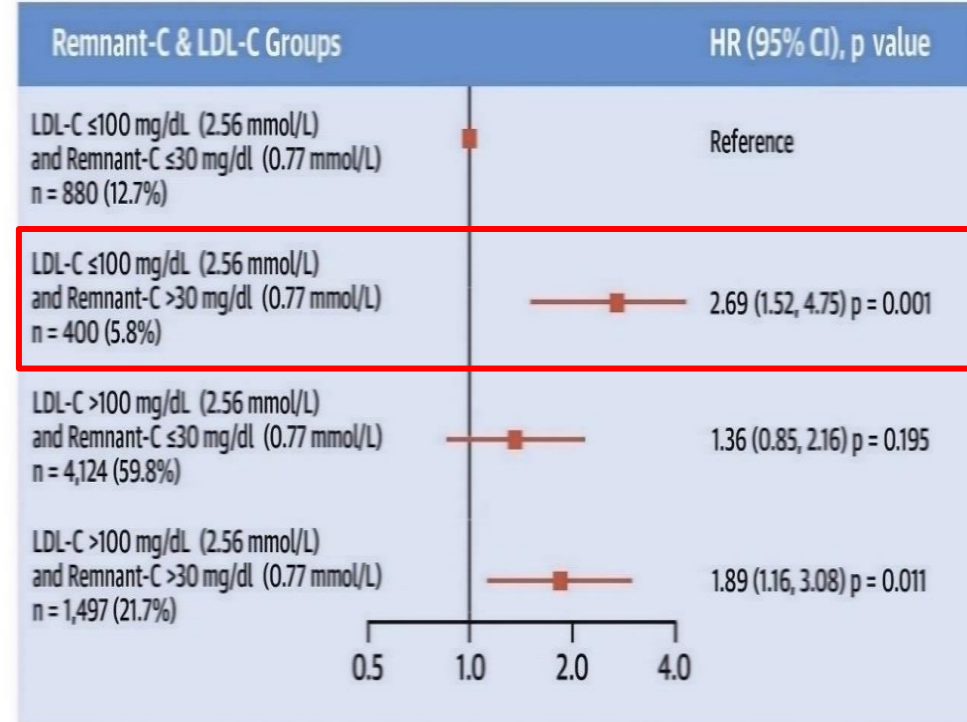
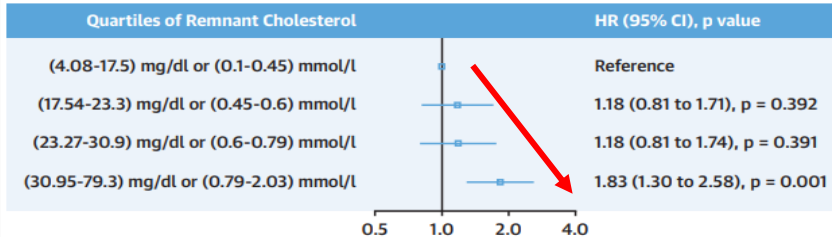
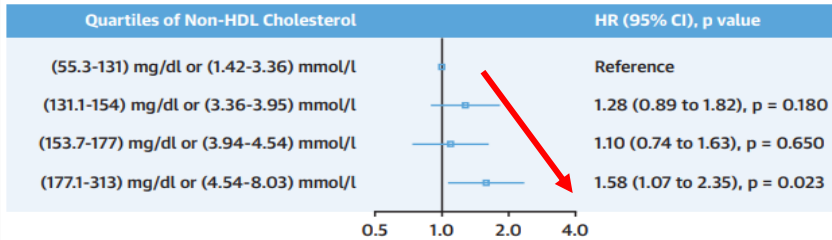
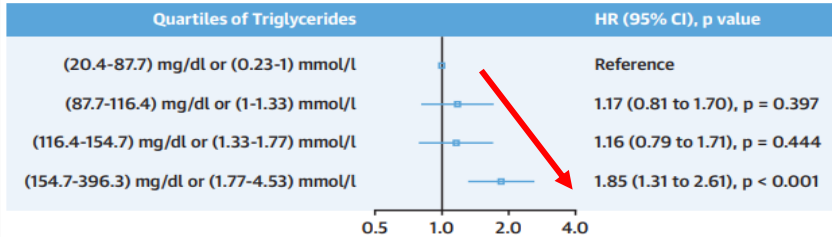


# Colesterol lipoproteic segons la trigliceridèmia a la població general

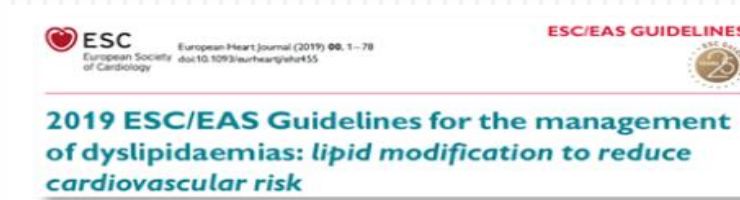


# Colesterol remanent i malaltia cardiovascular

## Cohort PREDIMED



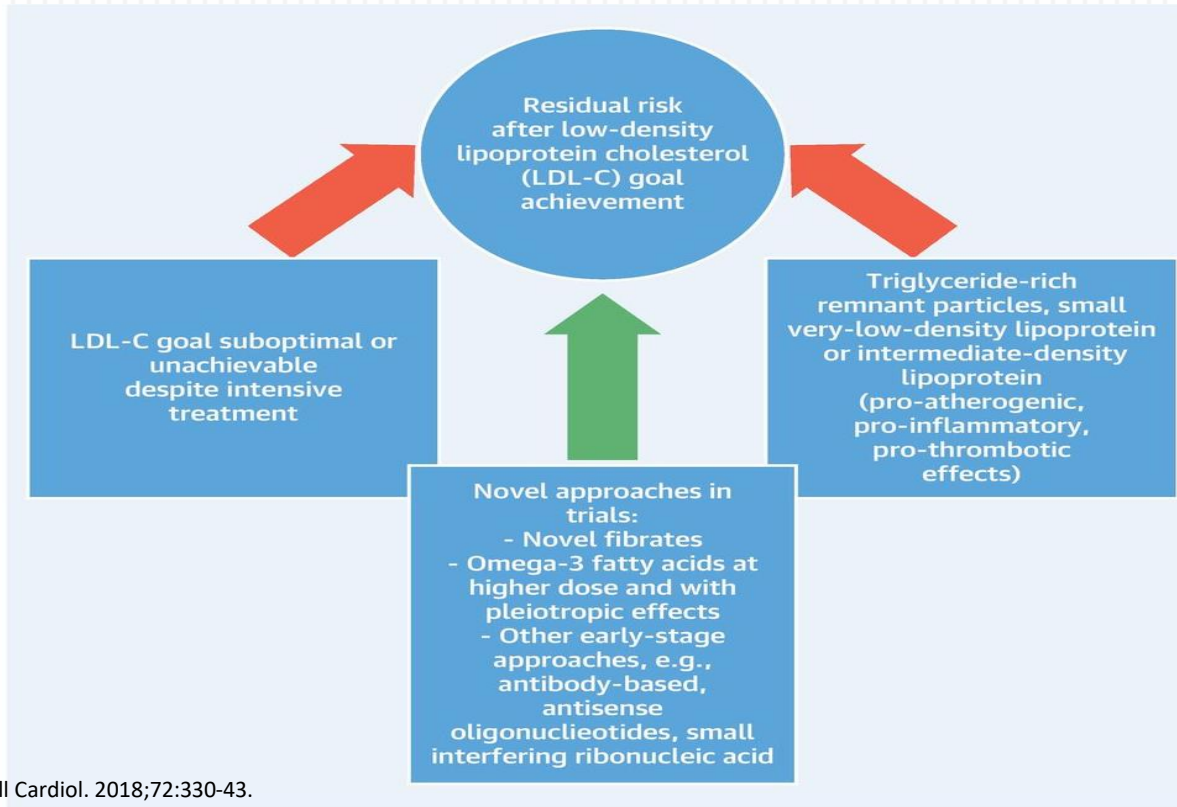
# Objectius terapèutics per reduir la MCV



RCV	Objectiu principal	Objectiu secundari*	
	cLDL	C-no HDL	ApoB
Molt alt	< 55 mg/dL + ↓ ≥50%	< 85 mg/dL	< 65 mg/dL
Alt	< 70 mg/dL + ↓ ≥50%	< 100 mg/dL	< 80 mg/dL
Moderat	< 100 mg/dL	< 130 mg/dL	< 100 mg/dL

\*Objectiu secundari en pacients amb hipertrigliceridèmia lleu-moderada (175 a 880 mg/dL), inclosos aquells amb obesitat o síndrome metabòlica, diabetis o malaltia renal crònica.

# Com podem reduir el risc residual d'origen lipídic?



## Actuals

- Fibrats (gemfibrocil, fenofibrat...)
- Àcid nicotínic
- AG $\omega$ -3 (EPA, EPA + DHA)
- Inhibidor de MTP (lomitapida)

## En desenvolupament

- Pemafibrat
- Antagonista apo C-III (volanesorsen)
- Inhibidors de ANGPL3
- Teràpia gènica LPL

# Estudis de prevenció cardiovascular amb fàrmacs hipotrigliceridemiants

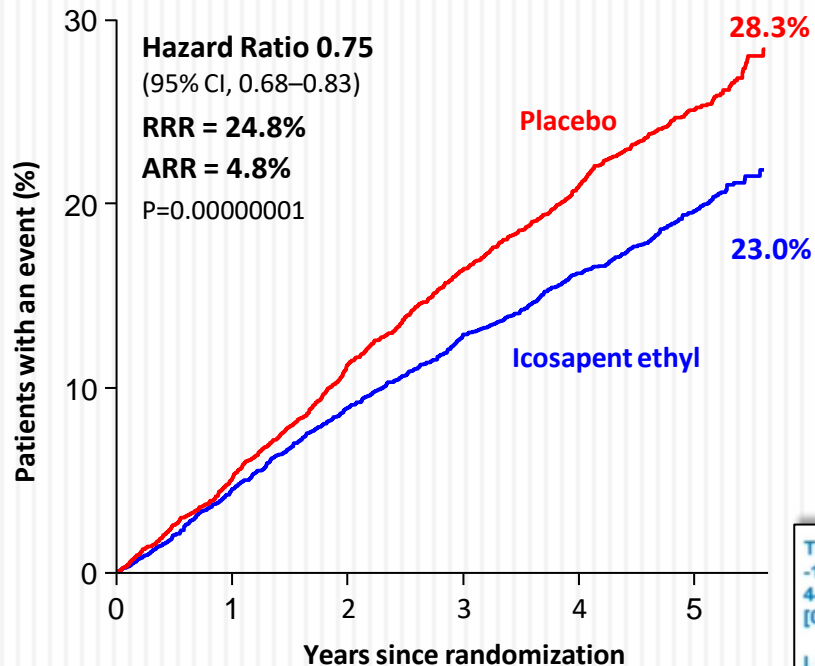
## Reducció del risc vs placebo en subgrups amb hipertrigliceridèmia

	<b>Trial (drug)</b>	<b>Entire Cohort Primary Endpoint</b>	<b>Lipid Subgroup Criterion</b>	<b>Subgroup Post-Hoc Primary Endpoint</b>
Fibrates	HHS (gemfibrozil)	-34% (<0.02)	TG >204 mg/dL LDL-C/HDL-C ratio >5.0	-72% (0.005)
	BIP (bezafibrate)	-7% (0.26)	TG ≥200 mg/dL	-39.5% (0.02)
	VA-HIT (gemfibrozil)	-22% (0.006)	TG ≥150 mg/dL	-27% (0.01)
	FIELD (fenofibrate)	-11% (0.16)	TG ≥204 mg/dL HDL-C <40 mg/dL (men) or <50 mg/dL (women)	-27% (0.005)
	ACCORD (fenofibrate)	-8% (0.32)	TG ≥204 mg/dL HDL-C ≤34 mg/dL	-31% (<0.05)
Niacin	AIM-HIGH (niacin-ER)	+2% (0.79)	TG ≥200 mg/dL HDL-C <32 mg/dL	-36% (0.032)
	HPS2-THRIVE (niacin-ER/PD1-I)	-4% (0.29)	NA	NA
EPA	JELIS (EPA 1.8 g/d)	-19% (0.011)	TG ≥150 mg/dL HDL-C <40 mg/dL	-53% (0.043)



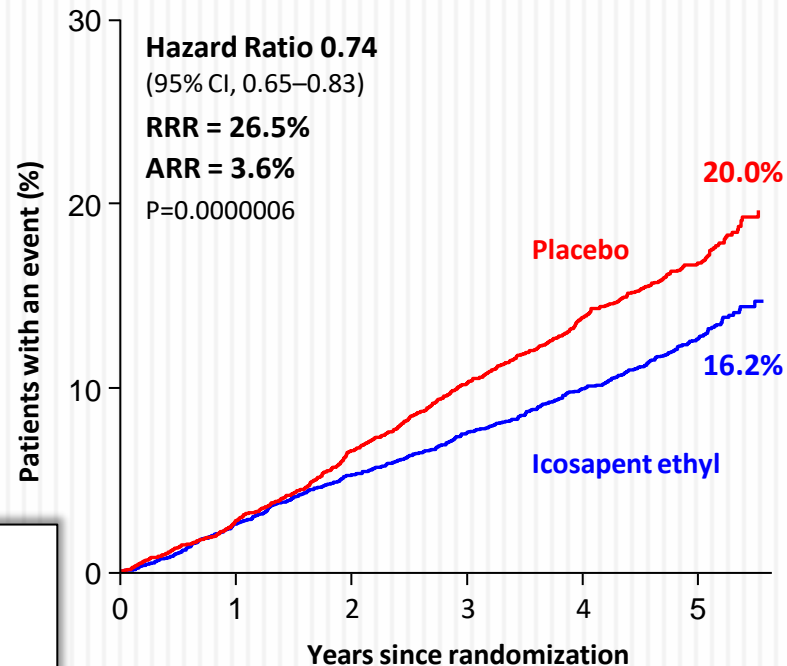
## Primary composite endpoint:

CV death, MI, stroke, coronary revasc, unstable angina



## Key secondary composite endpoint:

CV death, MI, stroke



**TG:**  
-19.7%  
44.5 mg/dl  
[0.50 mmol/L]

**LDL:**  
6.6% lower increase  
-> -5mg/dL lower

## KOWA TO DISCONTINUE K-877 (PEMAFIBRATE) "PROMINENT" CARDIOVASCULAR OUTCOMES STUDY



NEWS PROVIDED BY  
[Kowa Research Institute, Inc.](#) →  
Apr 08, 2022, 17:00 ET

SHARE THIS ARTICLE



RESEARCH TRIANGLE PARK, N.C., April 8, 2022 /PRNewswire/ -- Kowa Research Institute, Inc. announces the decision not to continue the Phase 3 PROMINENT study, taking into consideration the recommendations of the Data Safety Monitoring Board (DSMB). Based on the review of a planned interim analysis, the DSMB concluded that the primary endpoint was unlikely to be met. Notable safety concerns were not raised. Kowa Research Institute, Inc. will continue to pursue the potential of K-877 in new therapeutic areas, including nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), as encouraging data was revealed during the analysis of PROMINENT results.

Full data from the trial will be presented as soon as possible at a future conference.

**About K-877 (pemafibrate)**



# Estratègia hipolipemiant per reduir la MCV en pacients amb hipertrigliceridèmia



## 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)]. <sup>355</sup>	<b>I</b>	<b>B</b>
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) should be considered in combination with a statin. <sup>194</sup>	<b>IIa</b>	<b>B</b>
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins. <sup>305–307,356</sup>	<b>IIb</b>	<b>B</b>
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins. <sup>305–307,356</sup>	<b>IIb</b>	<b>C</b>

## 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
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)]. <sup>533</sup>	<b>I</b>	<b>A</b>
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. <sup>534–536</sup>	<b>IIb</b>	<b>B</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. <sup>84</sup>	<b>IIb</b>	<b>B</b>












**ESC**

European Society  
of Cardiology

European Heart Journal (2021) 42, 4791–4806  
doi:10.1093/eurheartj/ehab551

**SPECIAL ARTICLE**

## Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society

Henry N. Ginsberg<sup>1\*†</sup>, Chris J. Packard<sup>2†</sup>, M. John Chapman<sup>3</sup>, Jan Borén<sup>4</sup>, Carlos A. Aguilar-Salinas <sup>5,6</sup>, Maurizio Averna<sup>7</sup>, Brian A. Ference<sup>8</sup>, Daniel Gaudet <sup>9</sup>, Robert A. Hegele <sup>10</sup>, Sander Kersten<sup>11</sup>, Gary F. Lewis<sup>12</sup>, Alice H. Lichtenstein <sup>13</sup>, Philippe Moulin <sup>14</sup>, Børge G. Nordestgaard <sup>15,16</sup>, Alan T. Remaley<sup>17</sup>, Bart Staels <sup>18</sup>, Erik S.G. Stroes <sup>19</sup>, Marja-Riitta Taskinen<sup>20</sup>, Lale S. Tokgözoğlu <sup>21</sup>, Anne Tybjaerg-Hansen<sup>22,23,24,25</sup>, Jane K. Stock<sup>26</sup>, and Alberico L. Catapano<sup>27</sup>

## Estratègia de mires àmplies

