SERVICIO DE SALUD
DEL PRINCIPADO DE ASTURIAS

Objetivo de LDL de 55 mg/dl. Papel de los iPCSK9

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SOCIEDAD
ASTURIANA DE
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Impacto de la enfermedad cardiovascular aterosclerótica.

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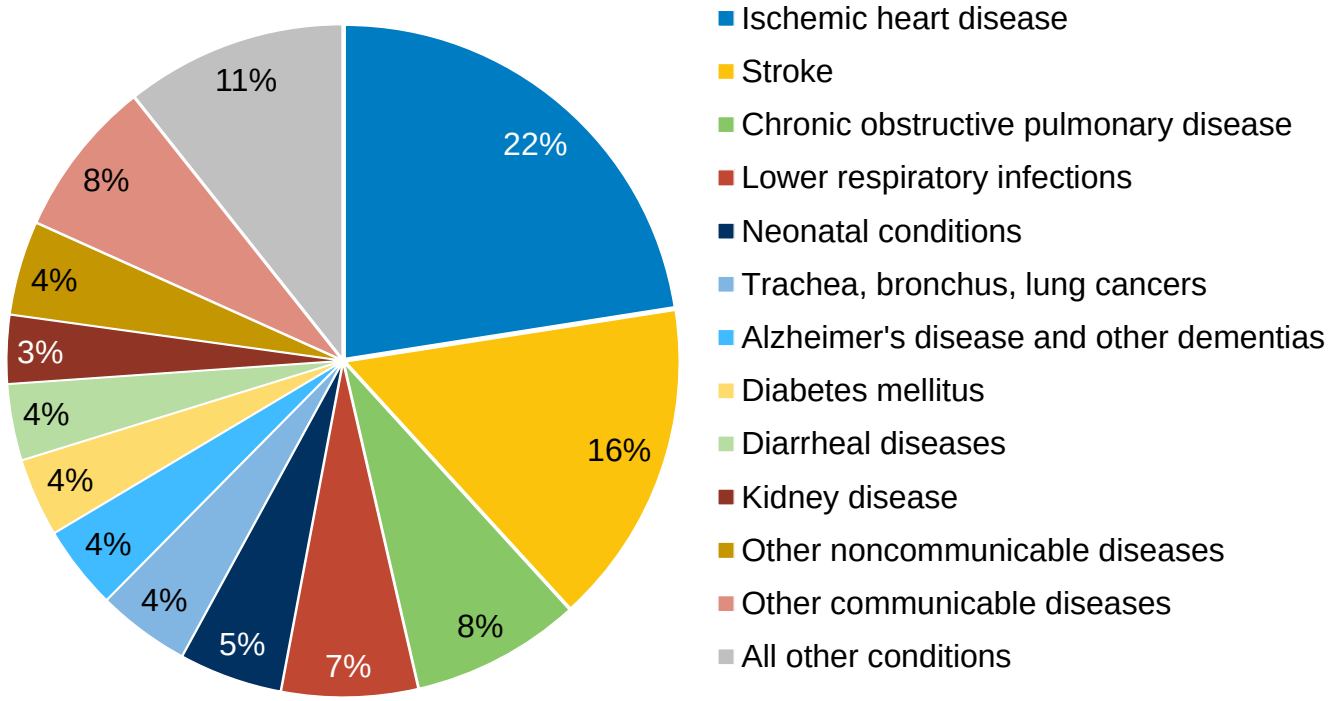
La enfermedad cardiovascular es la principal causa de muerte a nivel global.

WHO Global Health Estimates in 2019[1,2]

According to the WHO Global Health Estimates, in 2019:

- CVD accounted for more than 17.9 million worldwide deaths (32%):
  - ~ 8.9 million deaths due to ischemic heart disease
  - ~ 6.0 million deaths due to stroke

Leading Causes of Global Death in 2019[2,3]



Cardiovascular disease remains the leading cause of death globally, even during the period of the COVID-19 pandemic[1,2,4]

COPD= chronic obstructive pulmonary disease; CVD = cardiovascular disease; IHD= ischemic heart disease; WHO = World Health Organization.

1. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed July 7, 2021. 2. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed July 7, 2021. 3. World Health Organization. World Health Statistics 2021; May 20, 2021. 4. IHME. http://www.healthdata.org/. Accessed Dec 2, 2021.

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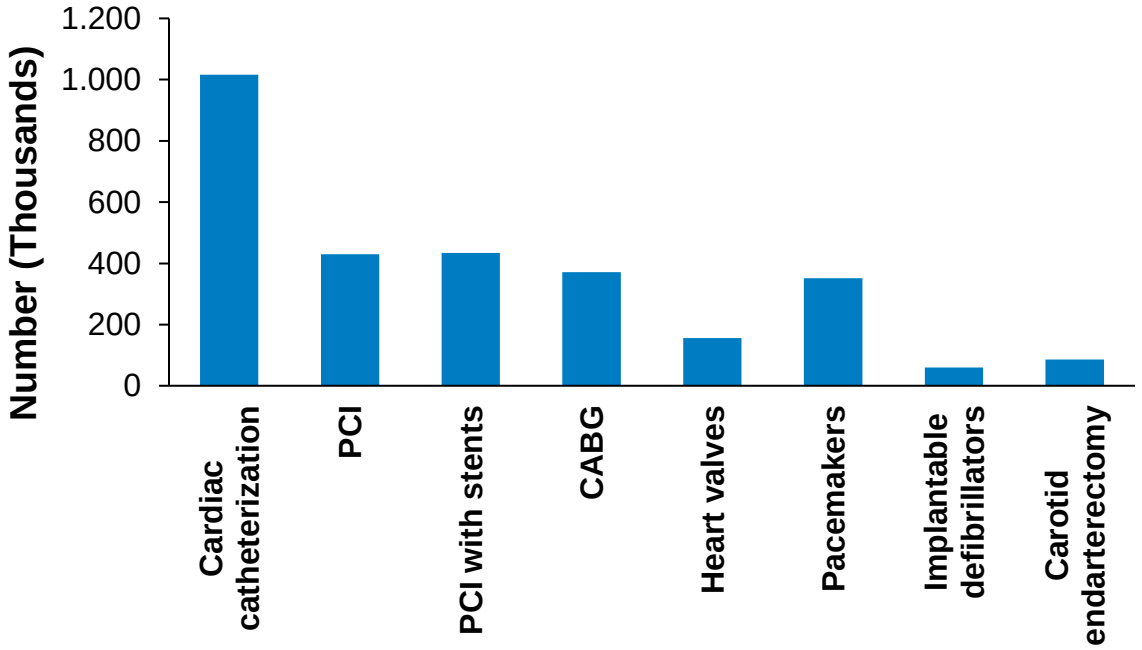
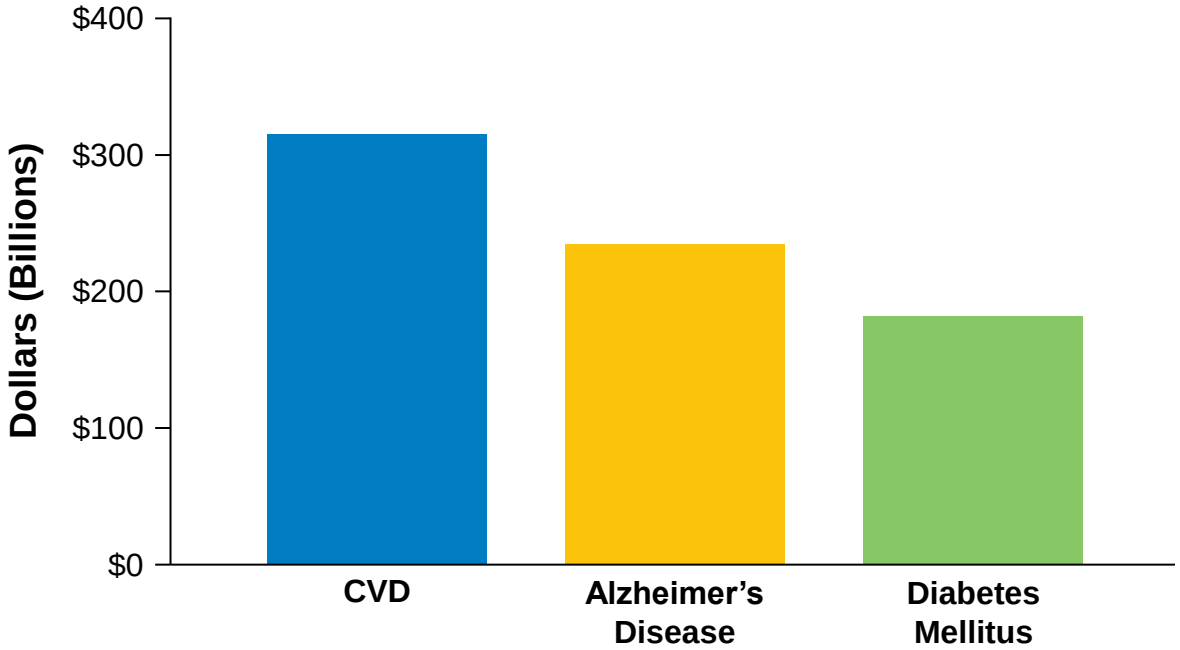
Pacientes con ECV frecuentemente requieren de procedimientos diagnóstico-terapéuticos, que además son más caros que la media.

Inpatient CV Operations/Procedures (2014) in the US[1]



- There were **~7,971,000** inpatient CV operations/procedures in the US in 2014[1]
- **CV procedures ranked the highest** in number among the 10 leading diagnostic groups in the US[1]

Comparative Direct Medical Costs (2015) in the US[2]



- Direct medical costs related to CVD are more extensive than medical costs related to any other disease[2]
- Direct medical costs of CVD in 2015 was **$318 billion** in the US and are projected to increase by **135%** to $749 billion in 2035[2]

Note: The information on this slide provides an example of costs, but the numbers may not be reflective of every region globally.

CABG = coronary artery bypass grafting; CV = cardiovascular; CVD = cardiovascular disease; PCI = percutaneous coronary intervention.

1. Virani SS, et al. *Circulation*. 2021;143:e254-e743. 2. American Heart Association. 2017. *Cardiovascular Disease: A Costly Burden for America — Projections Through 2035* (Consumer Report). Washington, DC.

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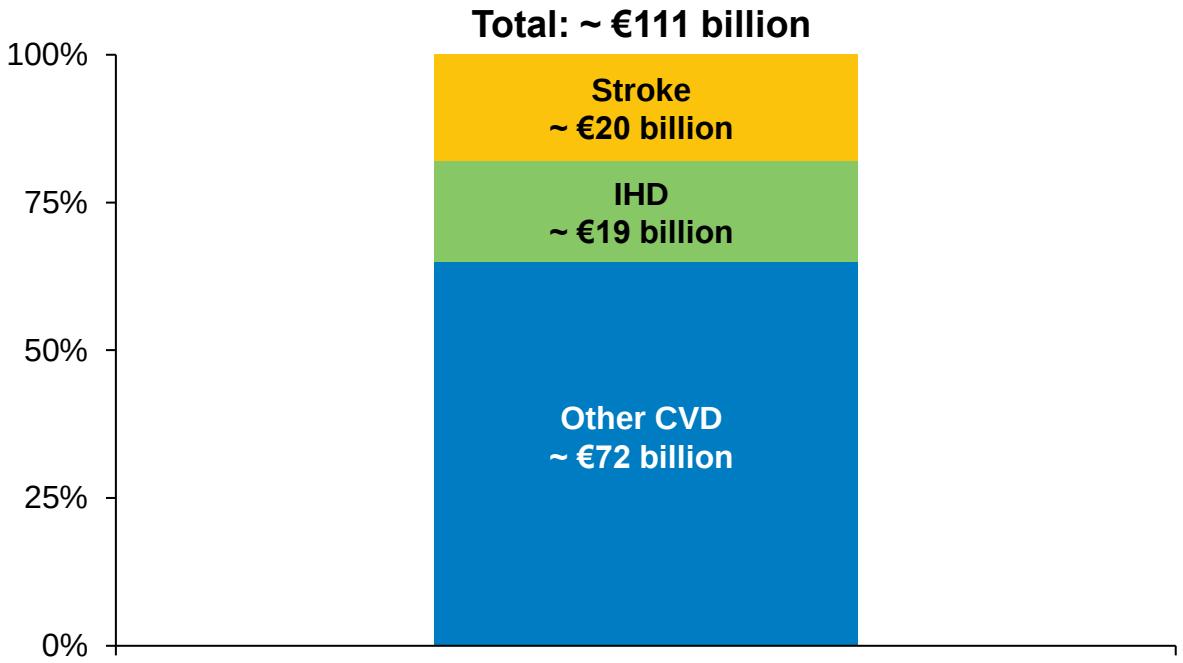
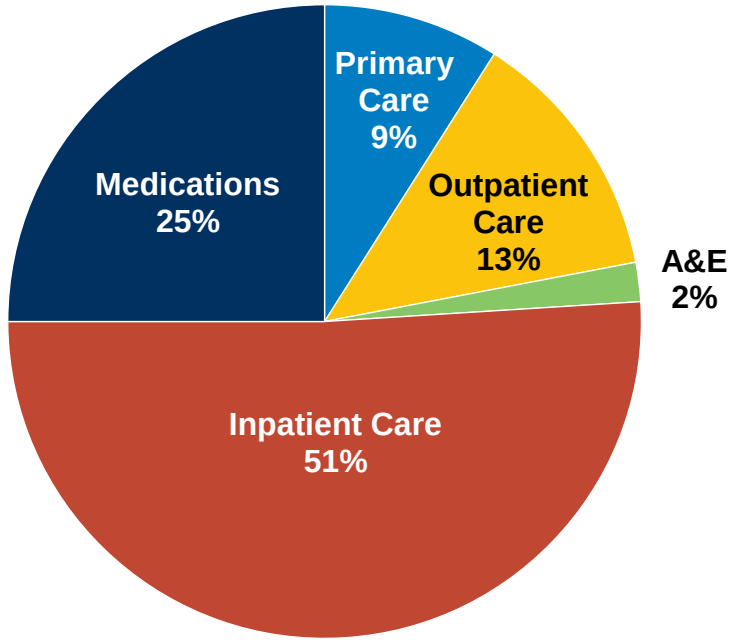
Los gastos sanitarios invertidos en enfermedad cardiovascular tienen un fuerte impacto económico.

Total CVD-related Direct Healthcare Costs (2015) in Europe



Total Healthcare Expenditures on CVD (2015), % in Europe



CVD healthcare costs in the EU are €111 billion, a cost per capita of €218 per annum, 8% of the total healthcare expenditure across the EU

Note: The information on this slide provides an example of costs, but the numbers may not be reflective of every region globally.
A&E = accident and emergency; CVD = cardiovascular disease; EU = European Union; IHD = ischemic heart disease.

Wilkins E, et al. 2017. *European Cardiovascular Disease Statistics 2017*. Brussels: European Heart Network.

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El síndrome coronario agudo es una patología común de elevada mortalidad y morbilidad.

Incidence and Prevalence

Every **40 seconds**, a person will have an MI[1,a]

7.29 million
Total global annual estimate for acute MI[2]

32 million
MIs and strokes occur worldwide every year[3]

605,000
Estimated annual incidence of new MIs in the US[1]

200,000
Estimated annual incidence of recurrent MIs in the US[1,b]

ACS Leads as a Global Cause of Death

≈ 14% of patients who experience an **MI will die as a result**[1,b]

~ 14.9 million (83%) of the ≈ 17.9 million deaths worldwide from CVDs are due to MI and stroke[4,5]

Mortality rates within 1 year after a first MI[1,c,d]

AGE	MORTALITY RATE
≥ 45 years	18% – 23%
45 to 64 years	3% – 10%
65 to 74 years	14% – 22%
≥ 75 years	19% – 31%

[a]AHA computation; [b]2005 to 2014 ARIC study of the NHLBI; [c]Unpublished NHLBI tabulation; [d]Pooled data from the FHS, ARIC, CHS, MESA, CARDIA, and JHS studies of the NHLBI (1995–2012).

ACS includes MI or unstable angina.[6]

ACS = acute coronary syndrome; AHA = American Heart Association; ARIC = Atherosclerosis Risk in Communities; CARDIA = Coronary Artery Risk Development in Young Adults; CHS = Cardiovascular Health Study; CVD = cardiovascular disease; FHS = Framingham Heart Study; JHS = Jackson Heart Study; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; NHLBI = National Heart, Lung, and Blood Institute.

1. Virani SS, et al. *Circulation*. 2021;143:e254-e743. 2. Roth GA, et al. *J Am Coll Cardiol*. 2017;70:1-25. 3. WHO. Integrated Management of Cardiovascular Risk. 2002.
4. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed July 7, 2021. 5. World Health Organization. https://www.who.int/news-room/fa sheets/detail/the-top-10-causes-of-death. Accessed July 7, 2021. 6. Mach F, et al. *Eur Heart J*. 2020;41:111-188.

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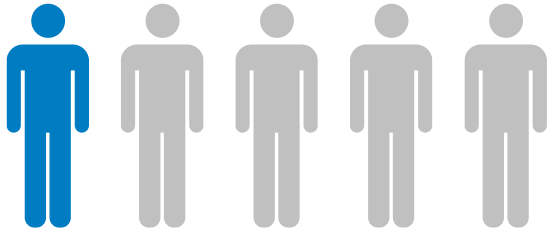
Elevadas cifras de rehospitalización así como impacto económico y sanitario tras un evento coronario agudo.



Nearly 1 in 5
patients with MI are rehospitalized (all causes) within **30 days**[1,*]

5.4 days
Mean length of stay for patients with MI[1,*]

18.1%
readmitted with a CV event (AMI, revascularization, UA, stroke within 1 year post discharge)[2,†]

~ 30%
higher relative risk for all-cause death and CV outcomes (recurrent MI, CVD death) after MI[3]

Increased costs after MI

Costs include:
Medical, inpatient, emergency room, ambulatory, office visit, outpatient visit, other medical, pharmaceutical[4]

For instance: Post-MI cost in the US at year 1 was **$52,752**[4,‡]

*National cohort of patients ≥ 65 years of age hospitalized for MI (N = 405,531) from Medicare and Medicaid Services Centers who were enrolled in the fee-for-service from 2010–2011[1]; †Type: Retrospective cohort analysis patient population: patients admitted with AMI from January 1, 2009 through December 31, 2017, identified from EMR in large health system covering 12 hospitals in Illinois N = 23,116 Prescription data available for 49% of patients[2]; ‡Systematic literature review of cost of illness studies in adults (aged ≥ 18 years) with any of the following CV events: MI, ischemic stroke (and undefined stroke), TIA, HF, UA, PCI, CABG, and PAD.[4]

Note: The information on this slide provides an example of costs, but the numbers may not be reflective of every region globally.
AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CV = cardiovascular; CVD = cardiovascular disease; EMR = electronic medical record; HF = heart failure; HFRS = Hospital Frailty Risk Score; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack; UA = unstable angina; US = United States.

1. Krumholz HM, et al. *Circulation*. 2014;130:966-975. 2. Liu Y, et al. Abstract presented at the World Congress of Cardiology; March 28-30, 2020; Chicago, IL. Abstract 007981. 3. Johansson S, et al. *BMC Cardiovasc Disord*. 2017;17:53. 4. Ryder S, et al. *Pharmacoeconomics*. 2019;37:895-919. 5. Kundi H, et al. *JAMA Cardiol*. 2019;4:1084-1091.

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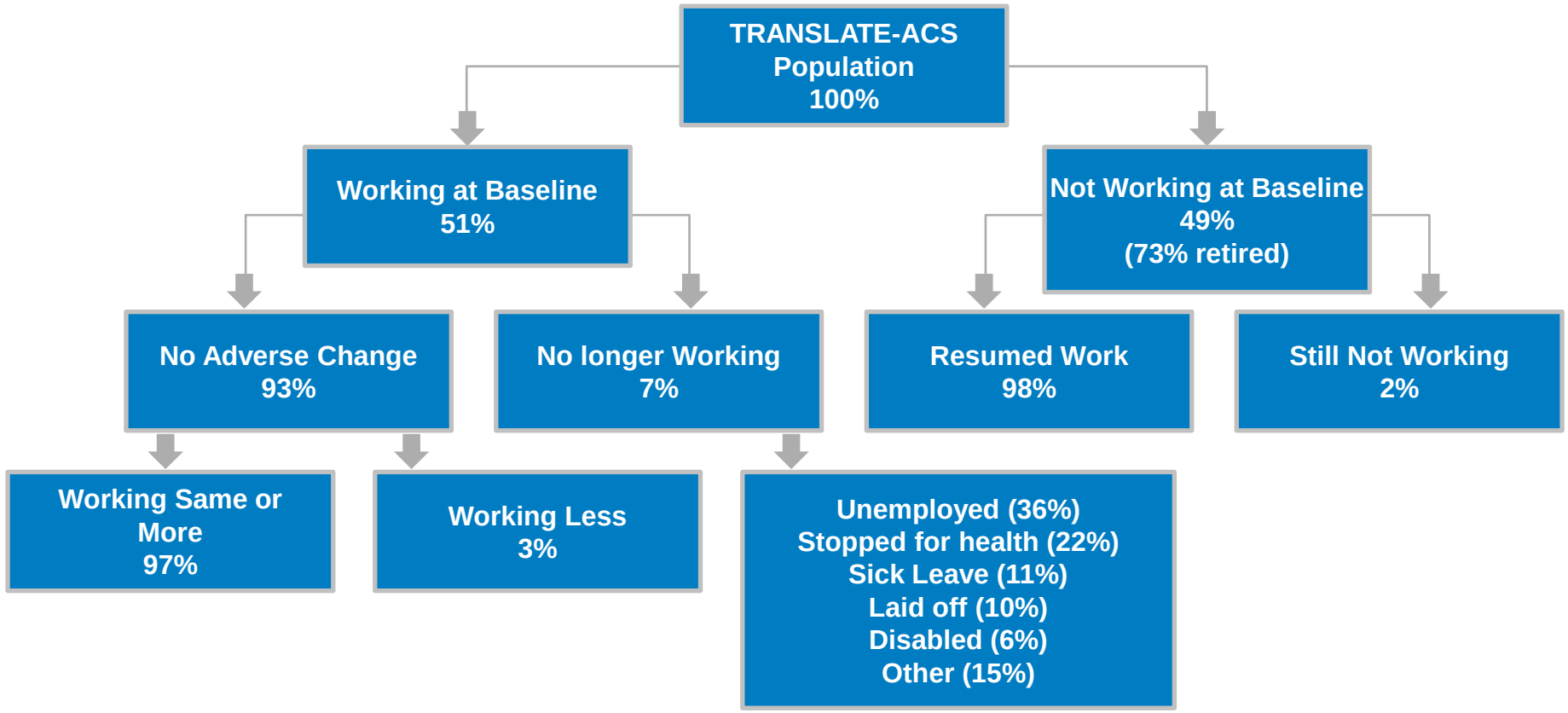
Los pacientes tras un evento coronario agudo experimentan más tasas de desempleo y prejubilaciones.

Patients:

n = 9,319 with MI

TRANSLATE-ACS study, longitudinal, observational registry of acute MI patients from 233 US hospitals

Goal: Assess adverse change in employment status at baseline and 1 year post-MI



The strongest factor associated with adverse change in employment in the 1 year after discharge was the number of readmissions within the first year (OR, 1.20; 95% CI, 1.09–1.32 per event)

Multivariate analysis of factors associated with adverse change in employment status at 1 year.
ACS = acute coronary syndrome; CI = confidence interval; MI = myocardial infarction; OR = odds ratio; TRANSLATE = Treatment with Adenosine Diphosphate Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome.

Warraich HJ, et al. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004528.

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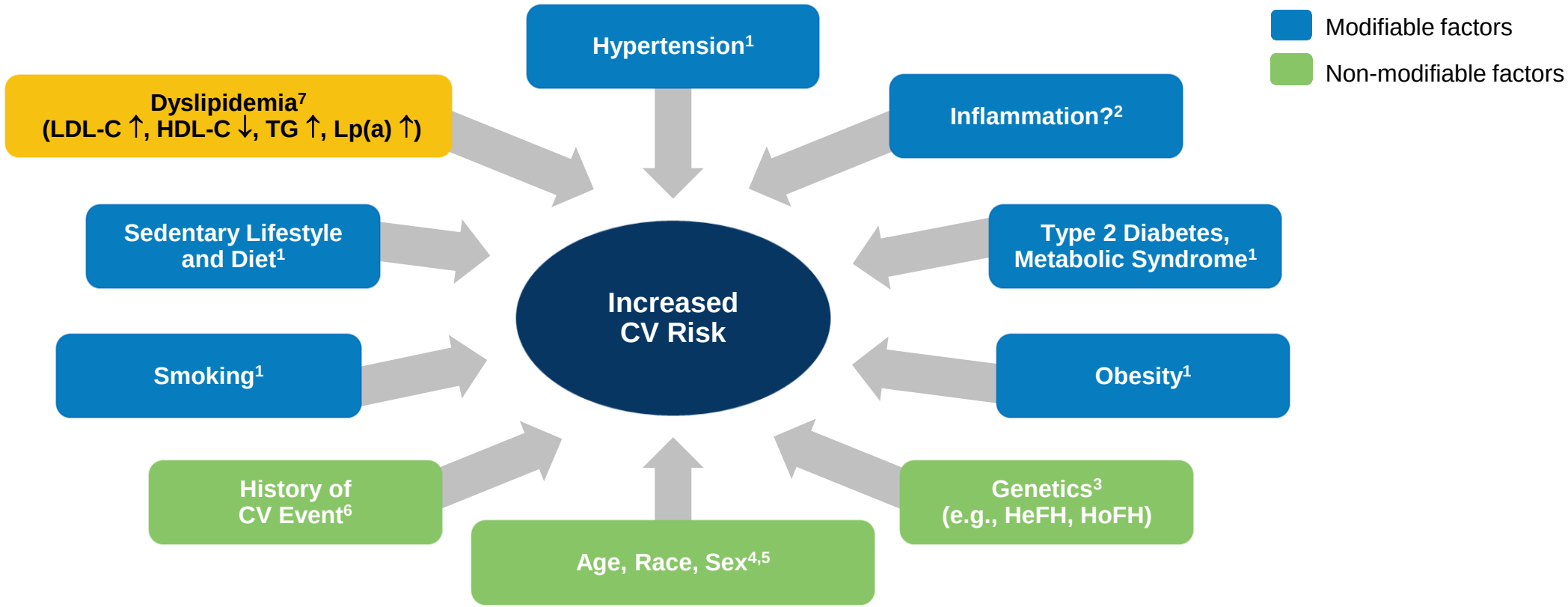
LDL es un factor de riesgo cardiovascular independiente.



LDL-C is a causal and modifiable risk factor for ASCVD[7,8]

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; HeFH = Heterozygous Familial Hypercholesterolemia; HDL-C = high density lipoprotein cholesterol; HoFH = Homozygous Familial Hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); TG = triglycerides.

1. WHO. 2011. *Global atlas on cardiovascular disease prevention and control*. Geneva: World Health Organization in collaboration with the World Heart Federation and the World Stroke Organization. 2. Ridker PM, et al. *Eur Heart J.* 2014; 35:1782-1791. 3. Sharifi M, et al. *Heart*. 2016;102:1003-1008. 4. Jellinger PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78. 5. Roger VL, et al. *Circulation*. 2012;125:e2-e220. 6. Stone NJ, et al. *J Am Coll Cardiol.* 2014;63:2889-2934. 7. Keenan TE, et al. *Curr Cardiol Rep*. 2013;396. 8. Ference BA et al. *Eur Heart J*. 2017;38:2459-2472.

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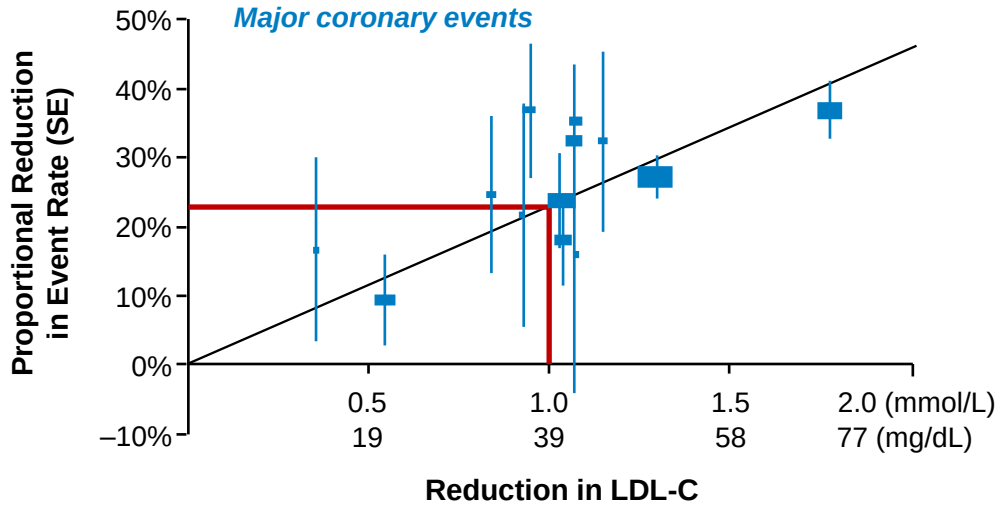
La reducción absoluta en valores de LDL se correlaciona con reducción relativa en eventos cardiovasculares.

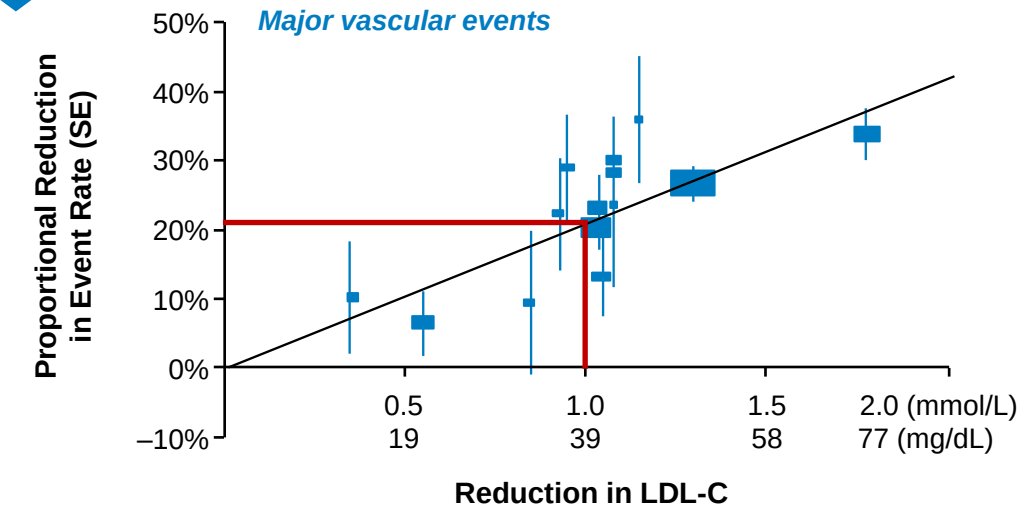
Mean Absolute LDL-C Reduction Is Linearly Related to Reduction in Incidence of Major Coronary and Vascular Events (Meta-analysis of 14 Statin Trials, 2005, N = 90,056)

1 mmol/L (39 mg/dL) reduction in LDL-C over 5 years was associated with:

23% reduction in major coronary events



21% reduction in major vascular events



Absolute reduction in LDL-C levels is the primary predictor of RRR

Major coronary events = nonfatal MI or CHD death. Major vascular events = the combined outcome of major coronary event, nonfatal or fatal stroke, or coronary revascularization. Each square represents a single trial plotted against mean absolute LDL-C reduction at 1 year, with vertical lines above and below corresponding to one SE of unweighted event rate reduction. Trials are plotted in order of magnitude of difference in LDL-C difference at 1 year. For each outcome, the regression line (which is forced to pass through the origin) represents weighted event rate reduction per mmol/L LDL-C reduction.
LDL-C = low-density lipoprotein cholesterol.

Cholesterol Treatment Trialists' (CTT) Collaborators. *Lancet*. 2005;366:1267-1278.

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Recomendaciones según guías de valores de LDL acordes a riesgo cardiovascular.

2018 AHA/ACC Guidelines
2 risk groups, including:

Very High-Risk

- **Multiple major ASCVD events** (recent ACS, history of MI, history of ischemic stroke, symptomatic PAD)

OR

- **1 major ASCVD event and multiple high-risk conditions** (eg, diabetes, hypertension)

2019 ESC/EAS Guidelines
5 risk groups, including:

Very High-Risk

- **Documented ASCVD**, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS,* stable angina, coronary revascularization,† stroke and TIA, and PAD‡
- **DM with target organ damage**, or at least three major risk factors, or early onset of type 1 DM of long duration (> 20 years)
- **Severe CKD** (eGFR < 30 mL/min/1.73 m^2)
- **A calculated SCORE ≥ 10%** for 10-year risk of fatal CVD
- **FH with ASCVD** or with another major risk factor

Statins are universally recommended as first-line therapy across guidelines and recommendations, followed by ezetimibe and/or PCSK9i

LDL-C THRESHOLD of 70 mg/dL

Threshold = trigger to intensify therapy by using or adding non-statin medications

LDL-C GOAL < 55 mg/dL AND ≥ 50% reduction from baseline

Additionally, for ASCVD patients on maximally tolerated statin experiencing a second vascular event within 2 years, a lower LDL-C goal of < 40 mg/dL (< 1.0 mmol/L) may be considered

*MI or UA; †PCI, CABG, and other arterial revascularization procedures; ‡unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with 2 major epicardial arteries having > 50% stenosis), or on carotid ultrasound.
ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass grafti CKD = chronic kidney disease; CT = computed tomography; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; EAS = European Atherosclerosis Society; eGFR = estimatec glomerular filtration rate; ESC = European Society of Cardiology; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery dis PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9 inhibitor TIA = transient ischemic attack; UA = unstable angina.

1. Grundy SM, et al. *J Am College Cardiol*. 2019;73:e285-e350. 2. Mach F, et al. *Eur Heart J*. 2020;41:111-188.

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75% de los pacientes con enfermedad cardiovascular establecida NO consiguen valores de LDL en objetivo pese a terapia con estatinas.

Patients:

N = 10,722

Population: ASCVD* with LDL-C ≥ 1.8 mmol/L at baseline

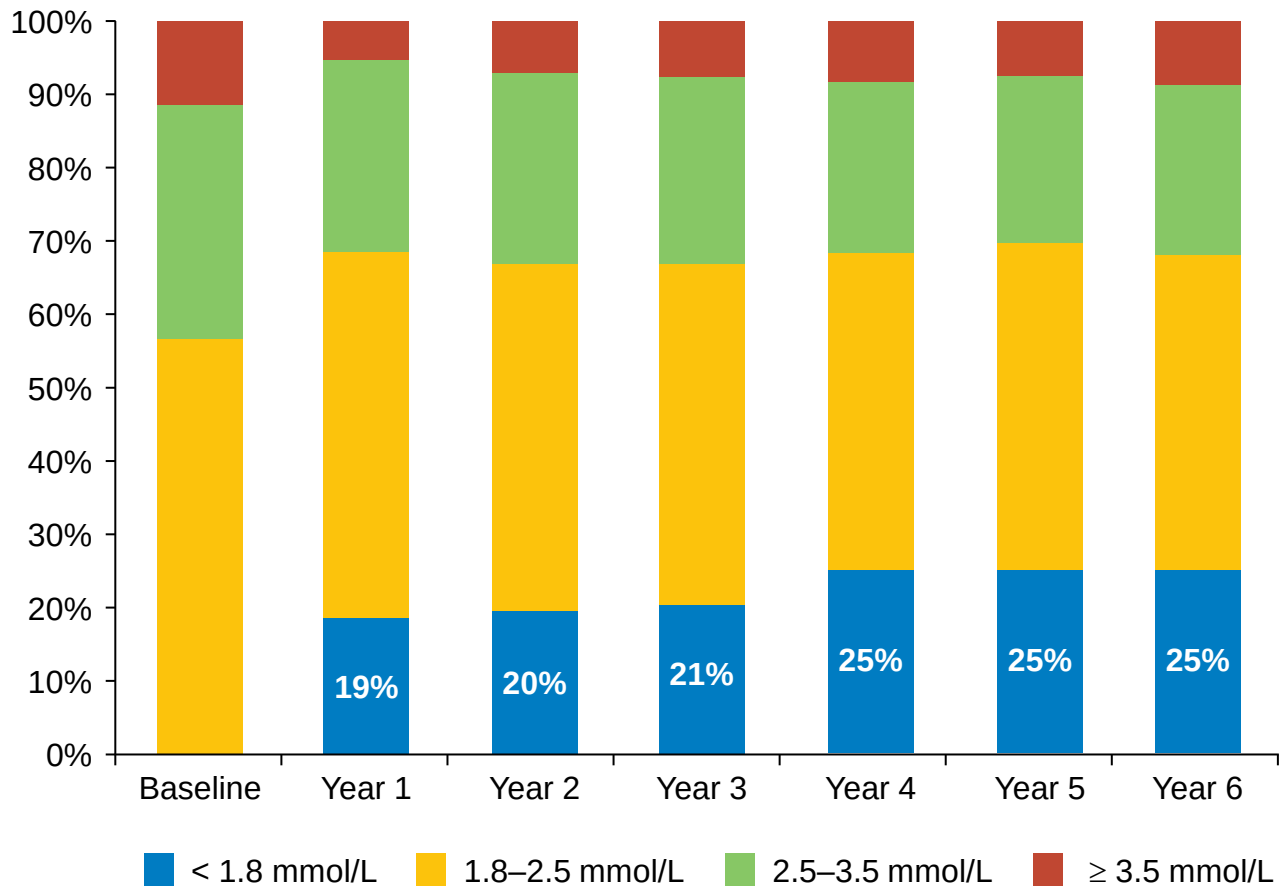
All received LLT (statins/ezetimibe)

Follow-up: 6 years

Primary Outcome: Composite: Cardiovascular death, MI, NS, hospitalization for UA, or coronary revascularization

Additional Observations: Change in LDL-C levels and statin use

Population-based Cohort Study in Denmark



LDL-C Measuring, Statin utilization

Proportion of patients receiving statin therapy decreased from 99% at study inclusion to 67% at 6 years

Of those taking statins, the percentage of patients on a high-intensity statin improved from 16% to 97% by the end of follow-up

Each year, approximately 25% of the study population did not have an LDL-C measurement

*Myocardial infarction, non-hemorrhagic stroke, or peripheral artery disease.

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; NS = non-hemorrhagic stroke; UA = unstable angina.

Sundbøll J, et al. *Thromb Res*. 2019;183:124-130.

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Menos de 40% de pacientes con un evento coronario agudo presentan valores de LDL < 70 mg/dl a los 4 meses.

Patients:

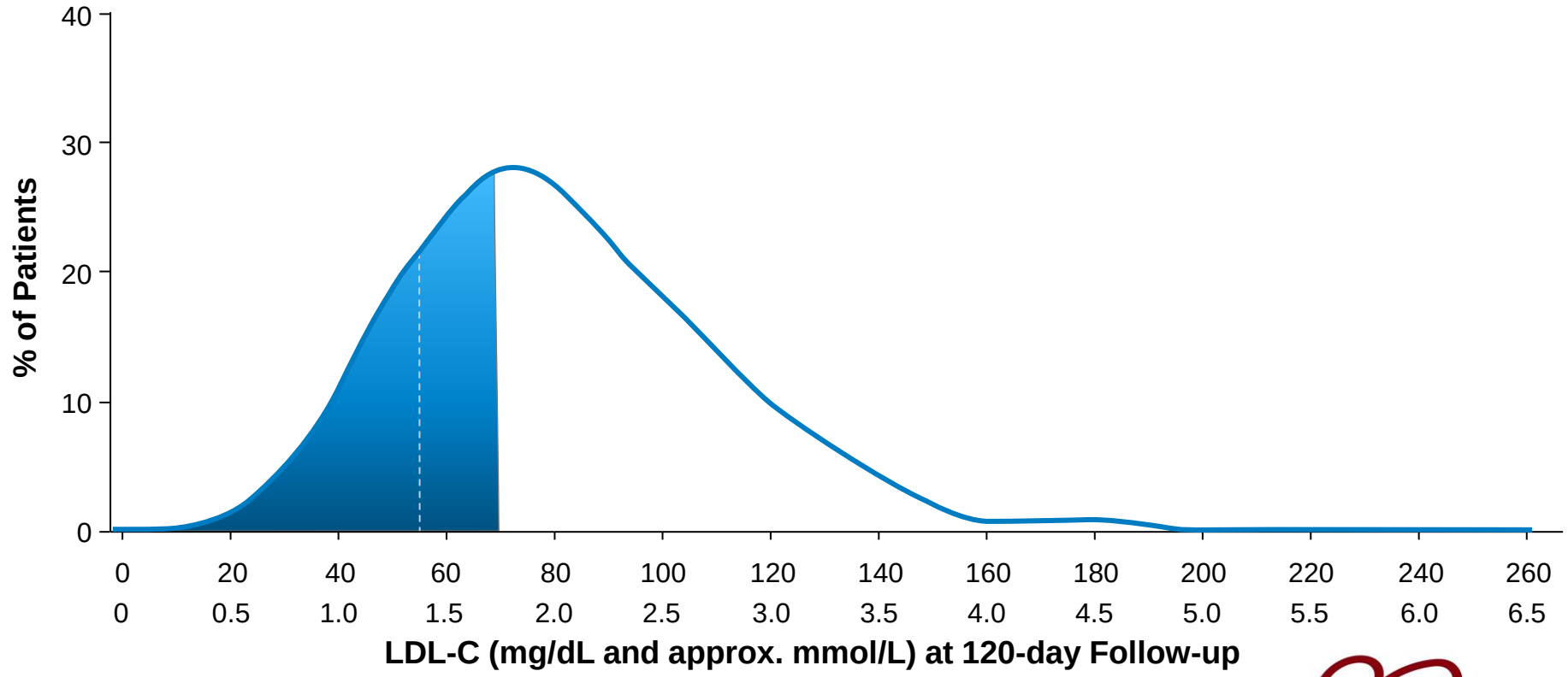
N = 10,661
CHD cohort, n = 6,794
ACS cohort, n = 3,867

Age:
CHD, 65.3 ± 10.8 years
ACS, 62.3 ± 12.1 years

Follow-up: 120 ± 15 days after admission

Prevalence of dyslipidemia and lipid target value attainment in patients with CHD and ACS

Multicenter, Observational Study: Dyslipidemia International Study (DYSIS II): Patients From 18 Countries With Either Stable CHD or ACS



Less than 25% of patients achieved an LDL-C level of < 55 mg/dL.

ACS = acute coronary syndrome; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

Gitt AK, et al. *Atherosclerosis*. 2017;266:158-166.

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Pacientes tras un infarto agudo de miocardio se encuentran infratrados con tratamiento hipolipemiante; menos del 40% con cifras de LDL< 70

Data From Two Italian Contemporary, Prospective, Real-World Registries of Patients With Stable CAD Post-MI Patients With LDL-C Levels (N = 3,074)

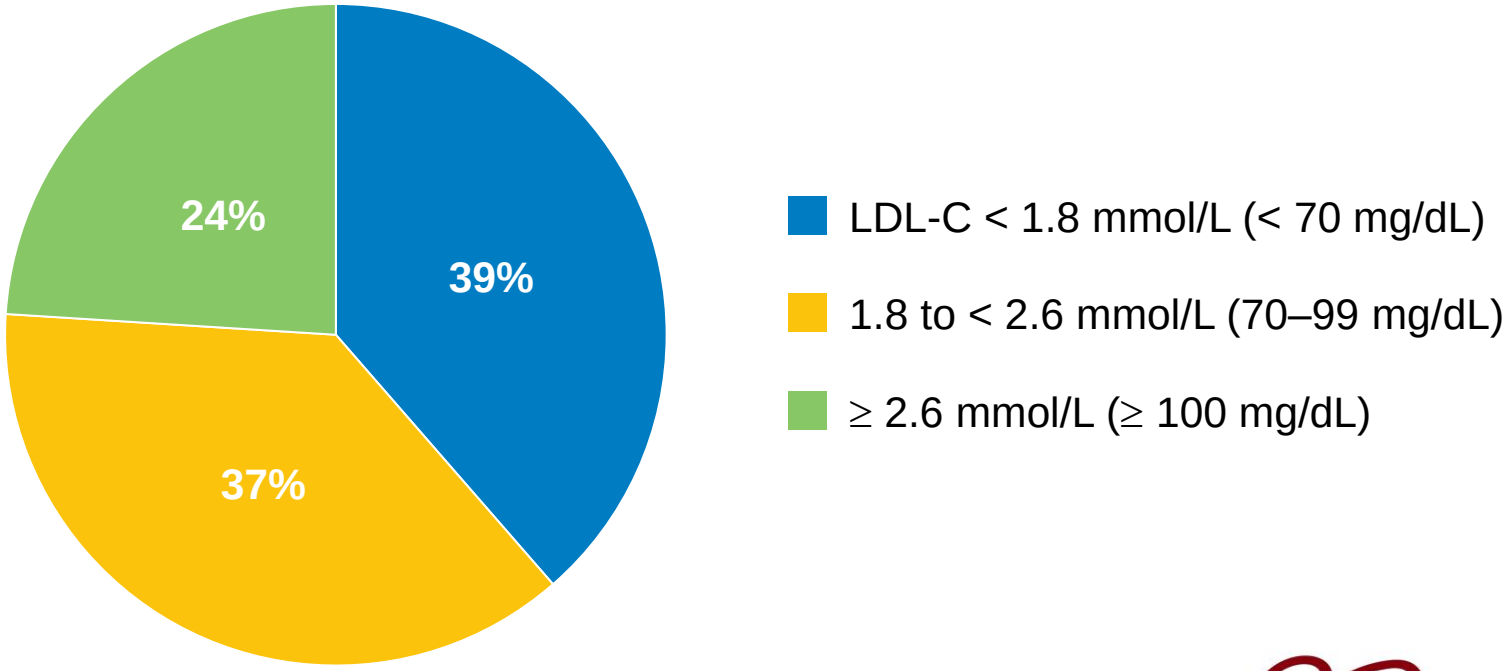
Patients were found to be on statin therapy more frequently (97.1%) when baseline LDL-C levels were ≤ 1.8mmol/L (70 mg/dL) compared to the other LDL-C groups ($P < 0.0001$)

Overall, low dose of statin was prescribed in 9.3%,while a high dose in 61.4% of patients

Statin plus ezetimibe therapy was used in less than 18% of patients in cohort

9.8% of patients were eligible for PCSK9i per the 2017 ESC/EAS Criteria*

% LDL-C Level Post-MI at Trial Enrollment



*European Heart Journal, vol. 38, no. 29, pp. 2245–2255, 2017.

CAD = coronary artery disease; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCSK9 = proprotein convertase subtilisin/kexin type 9 inhibitor.

Colivicchi F, et al. *Cardiovasc Ther*. 2020;2020:3856242.

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Perspectivas en recurrencia de eventos coronarios en la población con cifras objetivo de LDL< 70.

Patients:

N = 5,390

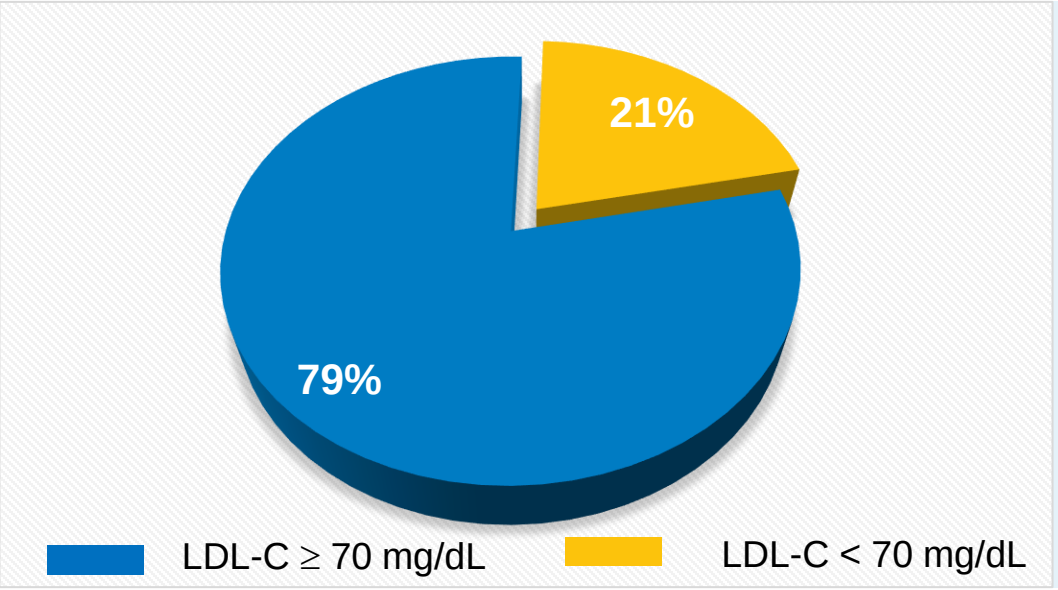
Population: Adults (≥ 45 years of age) with ASCVD[a] with LDL-C ≥ 70 mg/dL

Design: Retrospective, population-based cohort study

REGARDS study data were used to estimate the 10-year cumulative incidence of recurrent ASCVD events

CTTC meta-analysis rate ratios were used to estimate ASCVD risk reduction

Estimated US Adult Population (≥ 45 Years of Age) With a History of ASCVD[b]



About **14.7 million** US adults had a history of ASCVD, of whom **11.6 million** had LDL-C ≥ 70 mg/dL, based on data from 2009 to 2016

- A total of **2,823 million** ASCVD events were projected to occur over 10 years
- An estimated 634,000 ASCVD events (95% CI 542,000–737,000) could potentially be averted if all US adults with ASCVD achieved and maintained LDL-C < 70 mg/dL

[a]Including a history of CHD and stroke. [b]Figures (represented as percentages) in the pie chart has been rounded off to the nearest whole number.

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CI = confidence interval; CTTC = Cholesterol-Lowering Treatment Trialists' Collaboration; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; REGARDS = REasons for Geographic And Racial Differences in Stroke; US = United States.

McKinley EC, et al; [published online ahead of print October 2, 2021].*Cardiovasc Drugs Ther.* doi: 10.1007/s10557-021-07268-x.

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Seguridad de los valores muy bajos de LDL

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Remaining Questions You May Have Regarding Very Low LDL-C Levels

Are patients with very low LDL-C levels at a higher risk of hemorrhagic stroke?

If cholesterol is so important in the brain, would very low LDL-C levels lead to impaired cognitive function?

Studies have indicated there is an association between statin use and new-onset diabetes. Is this also the case for PCSK9 inhibitors?

Will my patient's steroid hormone levels be impacted by low LDL-C levels?

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

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Ictus hemorrágico

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Guías y recomendaciones relativas a ictus hemorrágico en pacientes con tratamiento hipolipemiante.

Guidelines and recommendations	Statement
2018 ACC/AHA Cholesterol Clinical Practice Guidelines[1]	• The frequency of hemorrhagic stroke with statins remains unclear
2018 AHA Scientific Statement[2]	• Available data in aggregate show no increased risk of brain hemorrhage with statin use in primary stroke prevention populations • An increased risk in secondary stroke prevention populations is possible, but the absolute risk is very small and the benefit in reducing overall stroke and other vascular events outweighs the risk
2018 AHA/ASA[3]	• Statins have an established role in secondary prevention and harbor promise in improving index stroke outcomes • High-intensity statin therapy is contraindicated or, when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used if tolerated in patients with ischemic stroke

*History of hemorrhagic stroke may modify the decision to use higher-intensity statin.

ACC, American College of Cardiology; AHA, American Heart Association; ASA, American Stroke Association.

1. Grundy SM, et al. *J Am Coll Cardiol*. 2019;18;139(25):e1082-e1143. **2.** Newman CB, et al. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38-e81. **3.** Powers WJ, et al. *Stroke*. 2018;49:E1-E345.

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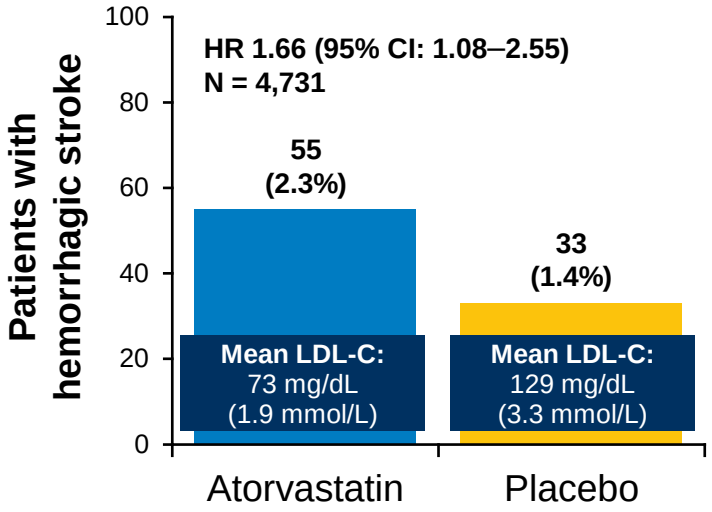
Resultados del estudio SPARCL y análisis posteriores.

Prospective study of patients with a history of stroke or TIA, baseline LDL-C 100–190 mg/dL (2.6–4.9 mmol/L), and no known CHD

SPARCL Post-Hoc Analysis[1]



SPARCL Secondary Analysis[2]

Baseline characteristics	Hazard ratio (95% CI)	*P* value
Male gender	2.21 (1.20–4.09)	0.01
Age, 10 y increment	1.40 (108–1.81)	0.01
Entry event = hemorrhagic stroke	8.38 (378–1856)	< 0.001
LDL-C (quartiles, atorvastatin group)	–	0.77
LDL-C < 52 mg/dL (< 1.3 mmol/L) (1st quartile, 12 events)*	–	–
LDL-C 52–65 mg/dL (1.3–1.7 mmol/L) (2nd quartile, 18 events)	1.26 (0.60–2.64)	0.54
LDL-C 66–92 mg/dL (1.7–2.4 mmol/L) (3rd quartile, 13 events)	0.97 (0.44–2.17)	0.94
LDL-C ≥ 93 mg/dL (≥ 2.4 mmol/L) (4th quartile, 45 events)	1.37 (0.63–2.98)	0.43

- **Atorvastatin 80 mg per day reduced the overall incidence of stroke, HR 0.84 (0.71–0.99)**
- **Post-hoc analysis showed an increase in the incidence of hemorrhagic stroke in the atorvastatin group (2.3% vs 1.4%)**

- **Further exploratory analysis showed no relationship between hemorrhagic stroke risk and baseline LDL-C level or recent LDL-C level in atorvastatin-treated patients**
- **Increased risk of hemorrhagic stroke was observed with male gender, increased age and hemorrhagic stroke as an entry event**

*Referent category.

CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TIA, transient ischemic attack; y, year.

1. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. *N Engl J Med*. 2006;355:549-559. **2.** Goldstein LB, et al. *Neurology*. 2008;70:2364-2370.

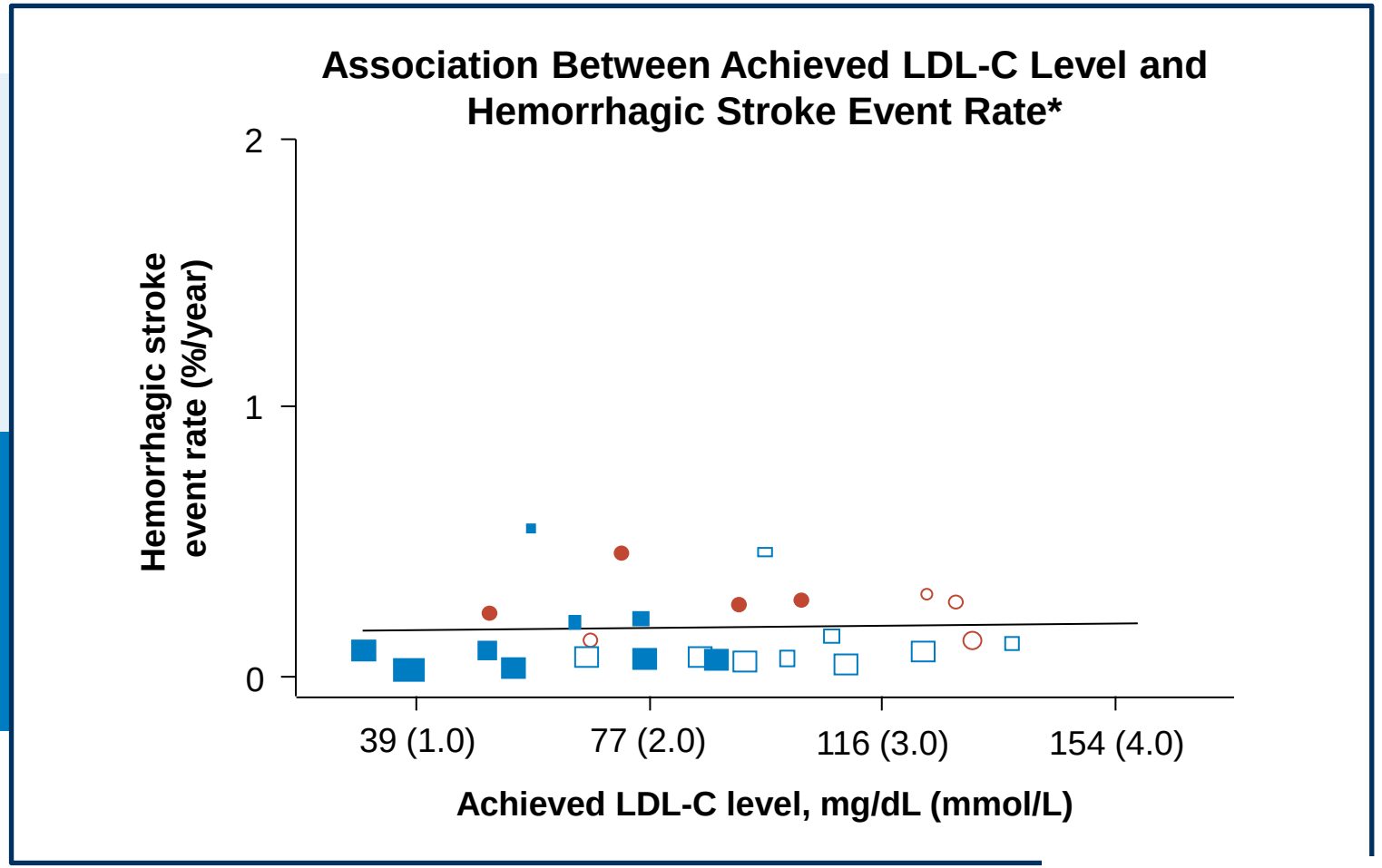
Non-Amgen

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Cifras de LDL inferiores a 30 mg/dl no se asociaron a ictus hemorrágico.

A meta-analysis of 222,149 participants in 23 randomized trials evaluated the association between achieved LDL-C levels and the risk of hemorrhagic stroke

There was no increase in hemorrhagic stroke risk with lower LDL-C, even at the very low level of 30 mg/dL (0.8 mmol/L) (Meta-regression slope 0.011, 95% CI: 0.068–0.089, *P* = 0.779)



*The size of each square on the graph indicates the weight of each trial, which was derived from the inverse of variance of the event rate of each trial.

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

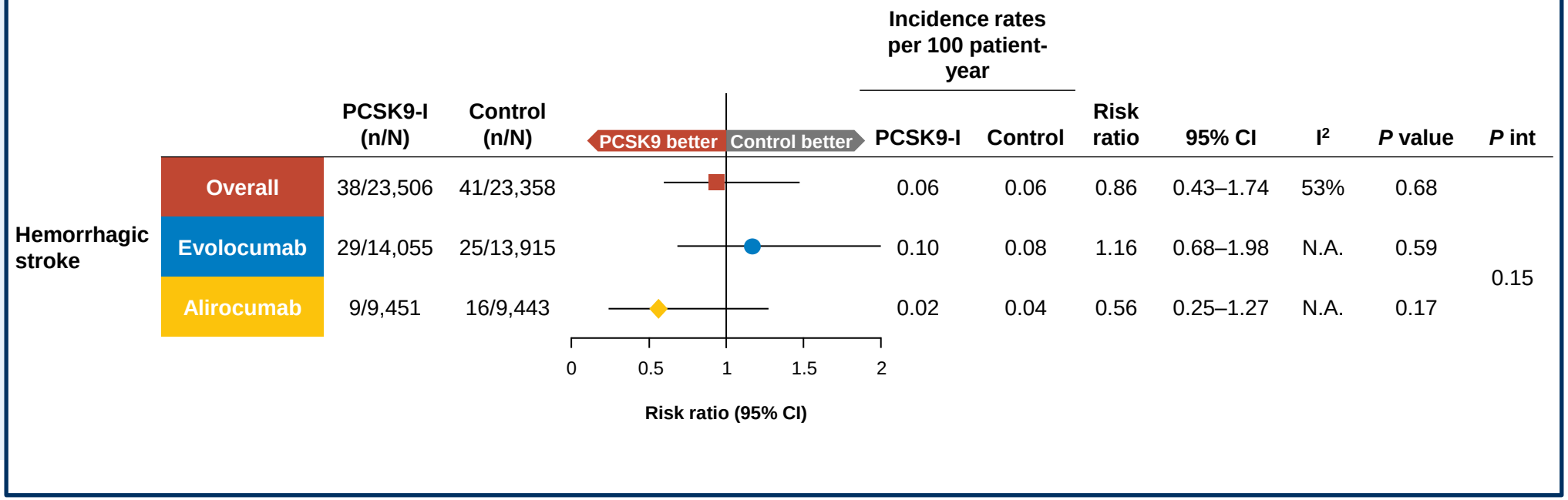
Shin J, et al. *Eur J Prev Cardiol*. 2019. Epub ahead of print.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

No se objetivó incremento del riesgo de ictus hemorrágico en metánalisis que incluyeron iPCSK9.

A meta-analysis of 39 RCTs comprising 66,478 patients examined the safety and efficacy of evolocumab or alirocumab vs placebo or other lipid-lowering therapies

Safety Endpoint for PCSK9 Inhibitors vs Control



There was no significant difference between PCSK9 inhibitors and controls for risk of hemorrhagic stroke

CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial.

Guedeney P, et al. *Eur Heart J*. 2019;0:1-9.

Non-Amgen

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

No se objetivó relación entre ictus hemorrágico y valores bajos de LDL en los subanálisis del estudio con alirocumab.

Hemorrhagic Stroke by Achieved LDL-C at 4 Months

	Month 4 LDL-C	n/N(%)
Prespecified analysis of ODYSSEY OUTCOMES study in patients with recent ACS with or without history of cerebrovascular disease	< 25 mg/dL (0.65 mmol/L)	2/3399 (0.1)
	25 to < 50 mg/dL (0.65 – 1.3 mmol/L)	3/3754 (0.1)
	50 to <70 mg/dL (1.30 – 1.8 mmol/L)	3/1090 (0.3)
	≥ 70 mg/dL (≥ 1.8 mmol/L)	4/1177 (0.3)

Risk of hemorrhagic stroke did not depend on achieved LDL-C levels in the alirocumab group, with a numerically lower proportion of patients in the lowest categories of achieved LDL-C experiencing this outcome

ACS = acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol

Jukema JW, et al. *Circulation*. 2019;140:2054-2062.

Deterioro cognitivo.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Guías y recomendaciones acerca de deterioro cognitivo en pacientes bajo tratamiento hipolipemiante.

Guidelines and recommendations	Statement
2018 ACC/AHA[1]	• The frequency of cognition impairment with statins is rare and unclear
2018 AHA Scientific Statement[2]	• There is no evidence that statins increase the risk for cognitive impairment • Prescribing information states that an association between cognitive impairment and statin has not been established

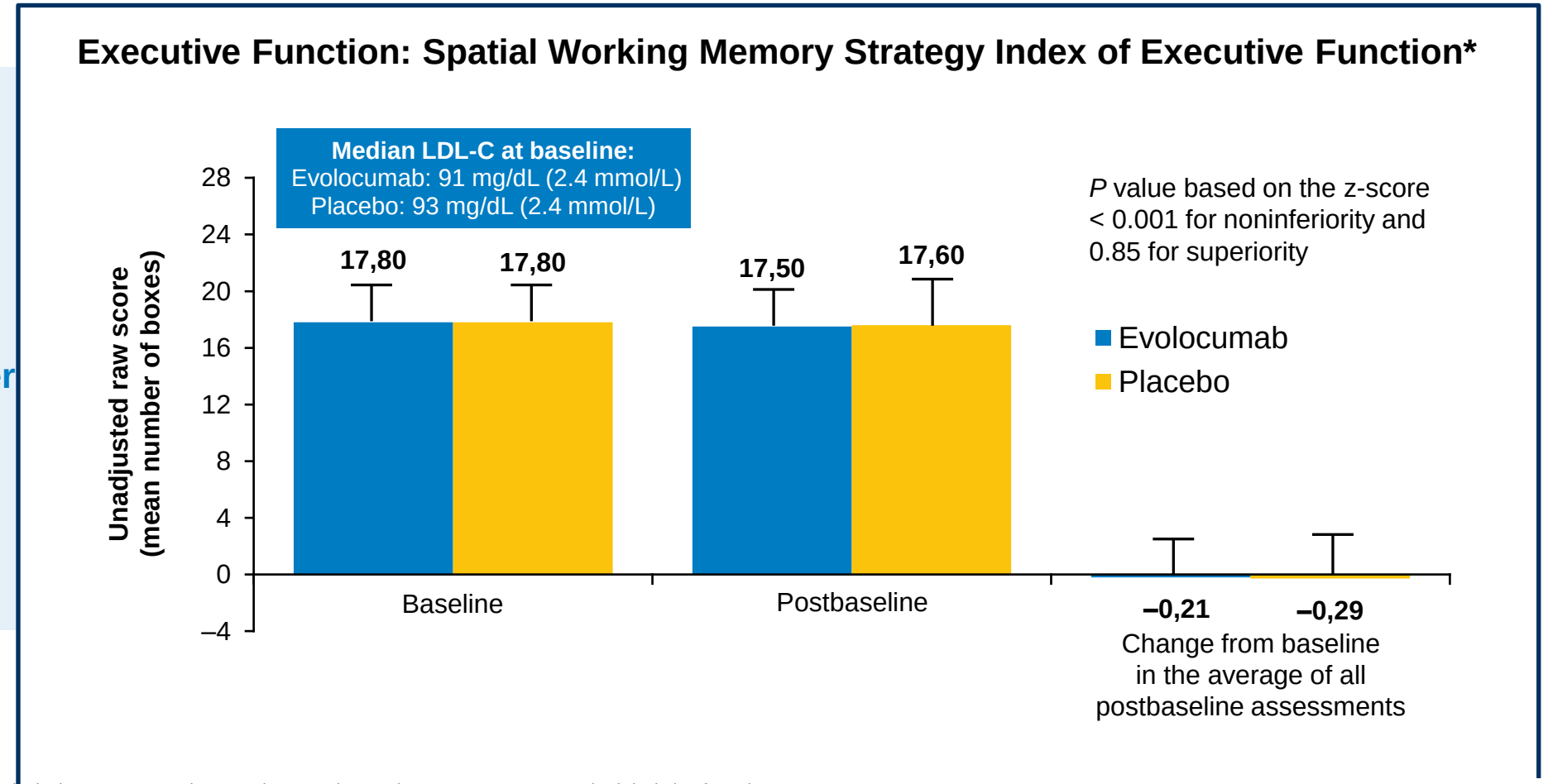
ACC, American College of Cardiology; AHA, American Heart Association.

1. Grundy SM, et al. *J Am Coll Cardiol*. 2019;18;139(25):e1082-e1143. **2.** Newman CB, et al. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38-e81.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

En el ensayo EBBINGHAUS no hubo diferencias en deterioro cognitivo entre el grupo de evolocumab y placebo.

The EBBINGHAUS study, comprising a subgroup of 1,204 patients from the FOURIER Trial, prospectively evaluated cognition among patients randomized to receive either evolocumab or placebo in addition to statin therapy



*Cognition was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). Error bars represent one standard deviation from the mean. Lower numbers indicate better performance. Negative numbers of change represent improvement in performance compared with the baseline.

EBBINGHAUS, Evaluating PCSK8 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C, low-density lipoprotein cholesterol.

Giugliano RP, et al. *N Engl J Med*. 2017;377:633-643.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

En el ensayo EBBINGHAUS no hubo diferencias en estado cognitivo en relación con valores de LDL.

Changes in CANTAB Endpoints Over Time, Stratified by Lowest-attained LDL-C Level*

Endpoint	Lowest-attained LDL-C level				
	Evolocumab group			Placebo group	
	< 25 mg/dL (< 0.6 mmol/L) (N = 661)	25–39 mg/dL (0.6–1 mmol/L) (N = 206)	≥ 40 mg/dL (≥ 1 mmol/L) (N = 115)	25–39 mg/dL (0.6–1 mmol/L) (N = 13)	≥ 40 mg/dL (≥ 1 mmol/L) (N = 969)
Primary endpoint: executive function (spatial working memory strategy index of executive function raw score)					
No. of patients with data	639	199	103	12	924
Change in score over time	–0.2 ± 2.7	–0.3 ± 2.9	–0.4 ± 2.6	0.7 ± 2.2	–0.4 ± 3.0
Secondary endpoints					
Working memory (spatial working memory between-errors raw score)					
No. of patients	639	199	103	12	924
Change in score over time	–0.5 ± 8.7	0.2 ± 9.6	–0.8 ± 8.1	0.4 ± 9.1	–0.6 ± 8.3
Episodic memory (paired associates learning raw score adjusted)					
No. of patients	638	199	103	12	919
Change in score over time	–0.3 ± 14.5	–0.6 ± 12.3	–1.0 ± 12.9	–3.4 ± 18.0	–0.2 ± 14.6
Psychomotor speed (median 5-choice retain time raw score)					
No. of patients	632	199	102	12	914
Change in score (in milliseconds) over time	5.5 ± 55.7	1.4 ± 66.2	7.8 ± 54.6	0.3 ± 65.1	1.8 ± 60.3
Exploratory endpoint: global composite score of CANTAB endpoints					
No. of patients	638	199	103	12	922
Change in z-score over time	0.02 ± 0.44	0.02 ± 0.42	0.03 ± 0.40	–0.02 ± 0.44	0.04 ± 0.47

Mean changes from baseline were similar between groups when patients were stratified according to lowest-attained LDL-C level

CANTAB, Cambridge Neuropsychological Test Automated Battery; EBBINGHAUS, Evaluating PCSK8 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Giugliano RP, et al. *N Engl J Med*. 2017;377:633-643.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Cifras de LDL inferiores a 25 mg/dl NO se asociaron con mayores tasas de empeoramiento en función cognitiva.

Pooled data from 14 phase 2 and 3 studies were analyzed to evaluate the safety of alirocumab in patients with at least two consecutive LDL-C values of < 25 or < 15 mg/dL (< 0.6 or < 0.4 mmol/L), with follow-up of up to 104 weeks

LDL-C levels of < 25 or < 15 mg/dL (< 0.6 or < 0.4 mmol/L) were not associated with an increased rate of neurologic and neurocognitive events

AEs of interest, % (n)	Pooled control (n = 1,894)	Alirocumab			
		Overall alirocumab (n = 3,340)	LDL-C ≥ 25 mg/dL (≥ 0.6 mmol/L) (n = 2,501)	LDL-C < 25 mg/dL (< 0.6 mmol/L) (n = 839)	LDL-C < 15 mg/dL (< 0.4 mmol/L) (n = 314)
Neurologic events	3.7 (71)	4.0 (134)	4.2 (105)	2.4 (20)	2.9 (9)
Peripheral neuropathy	3.3 (63)	3.2 (106)	3.4 (84)	1.7 (14)	2.2 (7)
Neurocognitive disorders	0.9 (17)	1.0 (32)	10 (26)	0.6 (5)	0.3 (1)
Amnesia	0.3 (5)	0.2 (6)	0.2 (5)	0.1 (1)	0
Aphasia	0	< 0.1 (2)	< 0.1 (1)	0.1 (1)	0
Confusional state	0.2 (3)	0.2 (8)	0.3 (7)	0.1 (1)	0
Dementia	0.1 (2)	< 0.1 (1)	0	0.1 (1)	0
Frontotemporal dementia	0	< 0.1 (1)	0	0.1 (1)	0.3 (1)

AE, adverse event; LDL-C, low-density lipoprotein cholesterol.

Robinson JJ, et al. *J Am Coll Cardiol*. 2017;69(5):471-482.

Nuevo diagnóstico de diabetes mellitus

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Guías y recomendaciones acerca de diagnóstico de DM de novo en pacientes bajo tratamiento betabloqueante.

Guidelines and recommendations	Statement
2018 ACC/AHA Cholesterol Clinical Practice Guidelines[1]	• Frequency of NODM increases if predisposing risk factors for DM are present, such as metabolic syndrome, or high-intensity statin therapy is present
2018 AHA Scientific Statement[2]	• Statin therapy modestly increases the risk for DM, but mechanism is not understood • Well established that statin therapy reduces CV events in those with or without DM • Increased risk of DM should not deter statin use in patients at sufficiently high CVD risk

- The increased risk may be limited to patients with prior risk factors for developing diabetes[3] and may be due to the effects of statins on HMGCR[4]

- In 2012, the FDA updated the prescribing information for all statins to include warnings on increases in HbA1c and fasting serum glucose levels reported with statins. The FDA stated "the cardiovascular benefits of statins outweigh these small increased risks"[5]

ACC, American College of Cardiology; AHA, American Heart Association; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; FDA, U.S. Food and Drug Administration; HbA1c, hemoglobin A1c; HMGCR, 3-hydroxy-3-methylglutaryl-coA reductase; NODM, new-onset diabetes mellitus.

1. Grundy SM, et al. *J Am Coll Cardiol*. 2019;18;139(25):e1082-e1143. **2.** Newman CB, et al. *Arterioscler Thromb Vasc Biol.* 2019;39(2):e38-e81. **3.** Ridker PM, et al. *Lancet.* 2012;380(9841):565-571. **4.** Swerdlow DI, et al. *Lancet*. 2015;385(9965):351-361. **5.** U.S. Food and Drug Administration. FDA Drug Safety Communication: important safety label changes to cholesterol lowering statin drugs. http://www.fda.gov/Drugs/DrugSafety/ucm 293101.htm. Accessed June 5, 2019.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Metanálisis refleja incremento de la incidencia de diabetes en pacientes tratados con estatinas de alta intensidad.

PREISS META-ANALYSIS[1]

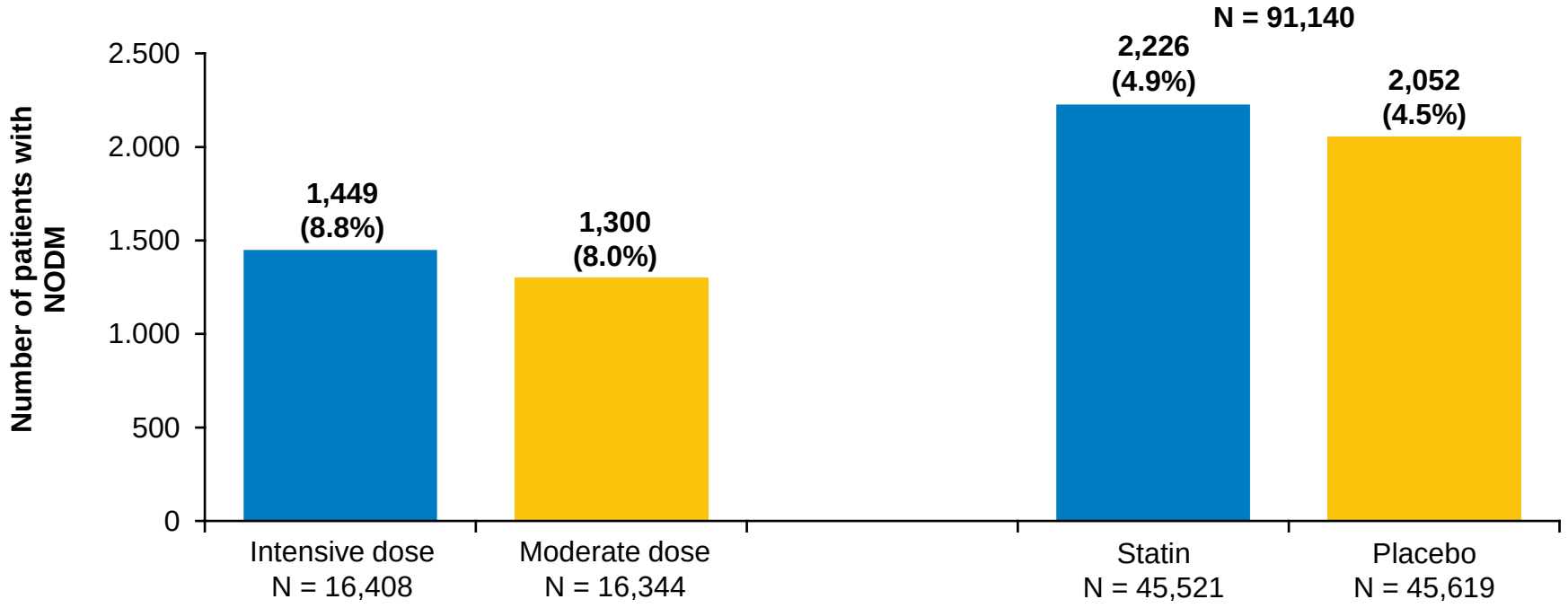
Meta-analysis of five randomized, controlled endpoint trials comparing intensive-dose statin with moderate-dose statin therapy and including > 1,000 participants who were followed up for > 1 year

OR (95% CI): 1.12 (1.04–1.22)

SATTAR META-ANALYSIS[2]

Meta-analysis of 13 randomized, controlled endpoint trials of statins with > 1,000 patients with identical follow-up in both groups and duration > 1 year

OR (95% CI): 1.09 (1.0–1.2)



CI, confidence interval; NODM, new-onset diabetes mellitus; OR, odds ratio.

1. Preiss D, et al. *JAMA.* 2011;305:2556-2564. **2.** Sattar N, et al. *Lancet*. 2010;375:735-742.

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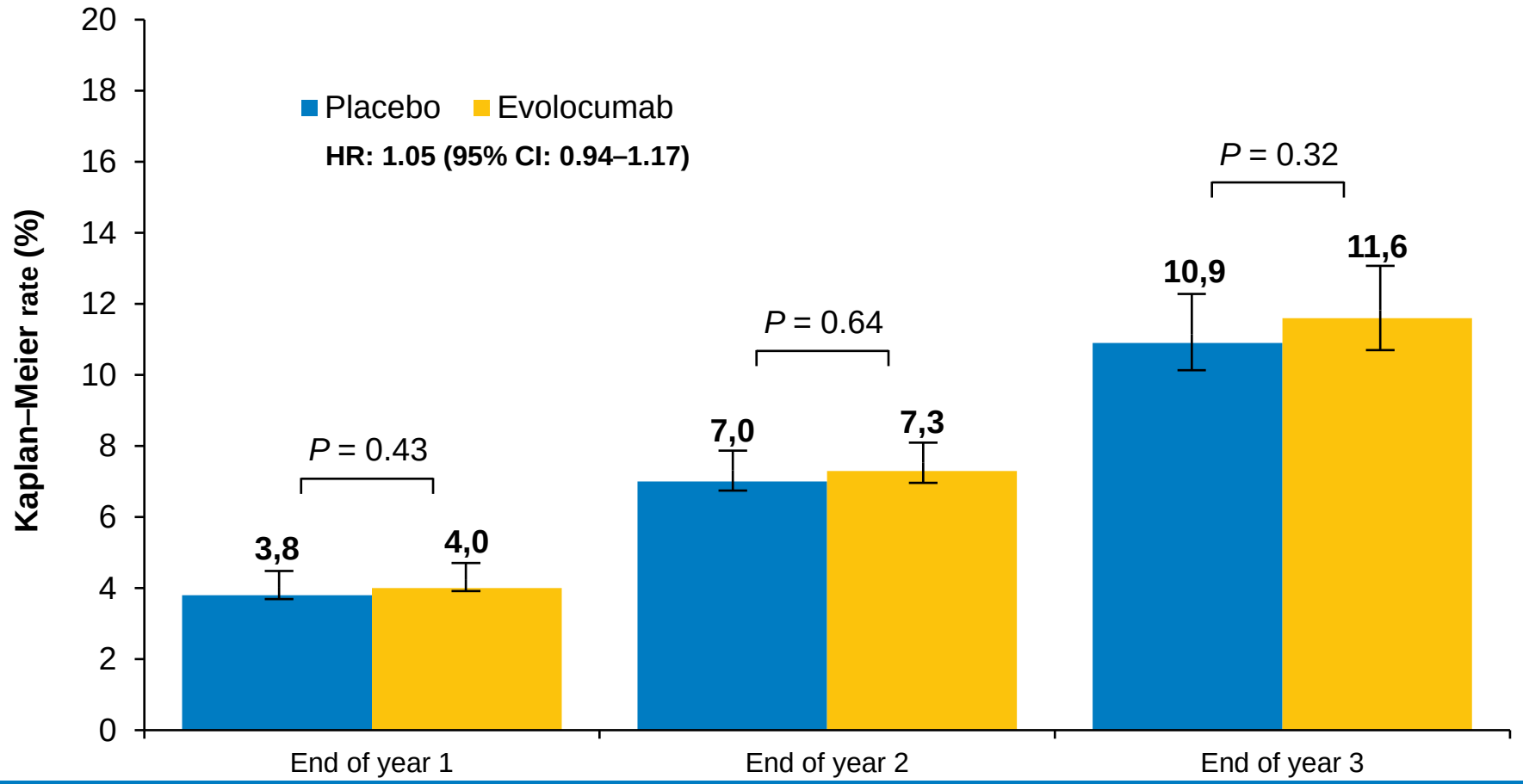
Incidencia de diabetes mellitus de novo en análisis entre grupos en el studio FOURIER.



Although numerically higher in the evolocumab arm compared with placebo, overall evolocumab did not increase the risk of NODM in patients without diabetes at baseline (8.0% vs 7.6%; HR 1.05, 95% CI 0.94–1.17).

At the end of years 1, 2, and 3 there was no difference in incidence of NODM between the 2 treatment arms.

*Data are the

Note: Post-hoc analyses of patients with pre-diabetes at baseline showed between treatment group difference in the incidence of NODM of HR 1.00 (95% CI: 0.89–1.13).

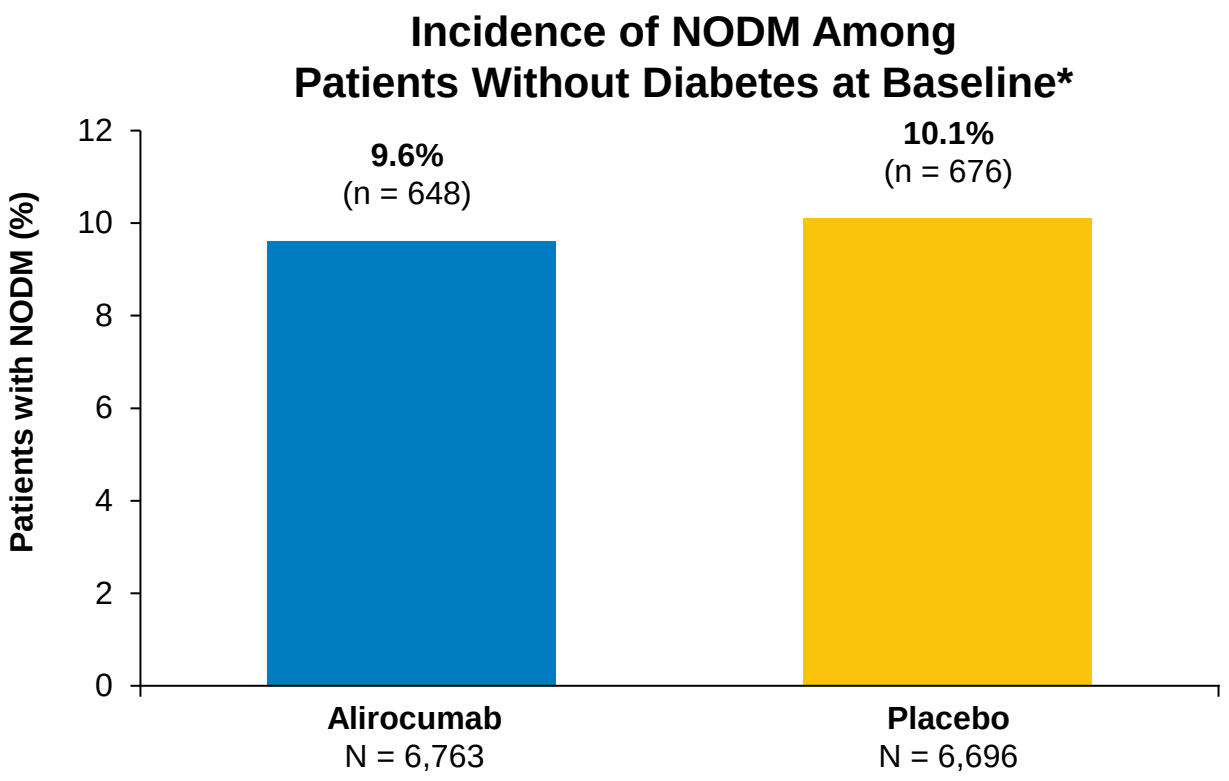
CI, confidence interval; HR, hazard ratio; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; NODM, new-onset diabetes mellitus.

Sabatine MS, et al. *Lancet Diab Endocrinol*. 2017;12:941-950.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

El ensayo ODYSSEY no reflejó asociación estadísticamente significative entre DM y tratamiento con alirocumab.

The ODYSSEY OUTCOMES trial was a multicenter, randomized, double-blind, placebo-controlled trial of 18,924 patients with ACS on statin therapy who were randomized to receive alirocumab or matching placebo



*NODM was defined according to the presence of one or more of the following, with confirmation of the diagnosis by blinded external review by experts in the field of diabetes: an AE report, a new prescription for diabete a glycated hemoglobin level of at least 6.5% on two occasions (and a baseline level of < 6.5%), or a fasting serum glucose level of at least 126 mg/dL (7 mmol/L) on two occasions (and a baseline level of < 126 mg/dL [<

ACS, acute coronary syndrome; AE, adverse event; LDL-C, low-density lipoprotein cholesterol; NODM, new-onset diabetes mellitus; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab.

Schwartz GG, et al. *N Engl J Med*. 2018;379:2097-2107.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

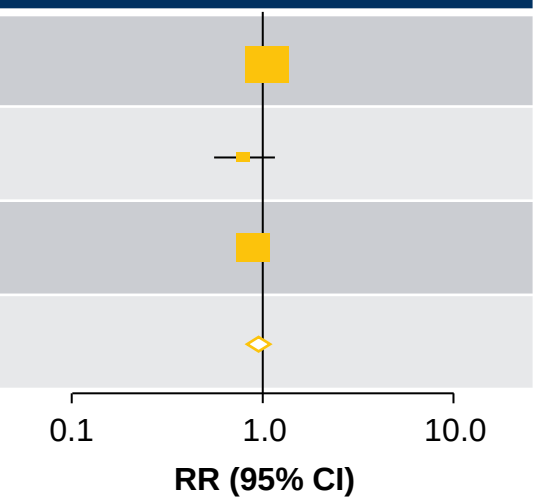
En metanálisis de ensayos clínicos recientes, niveles bajos de LDL (<20 mg/dl) NO se asociaron con incremento de riesgo de DM.

Safety outcome	Patients with event, no.		Meta-analysis data	
	Experimental arm	Control arm	RR (95% CI)	*P* value
NODM	1,272	1,320	0.97 (0.90–1.05)	0.46

LDL-C lowering was not associated with an increased risk of NODM in any of the trials individually or when met-analyzed

NODM

Trial	RR (95% CI)
IMROVE-IT	1.05 (0.95–1.15)
FOURIER	0.79 (0.54–1.16)
REVEAL	0.89 (0.79–1.00)
Overall	0.97 (0.90–1.05)



CI, confidence interval; CV, cardiovascular; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; IMPROVE-IT, Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin; LDL-C, low-density lipoprotein cholesterol; NODM, new-onset diabetes mellitus; REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification; RR, risk ratio.

Sabatine MS, et al. *JAMA Cardiol*. 2018;3(9):823-828.

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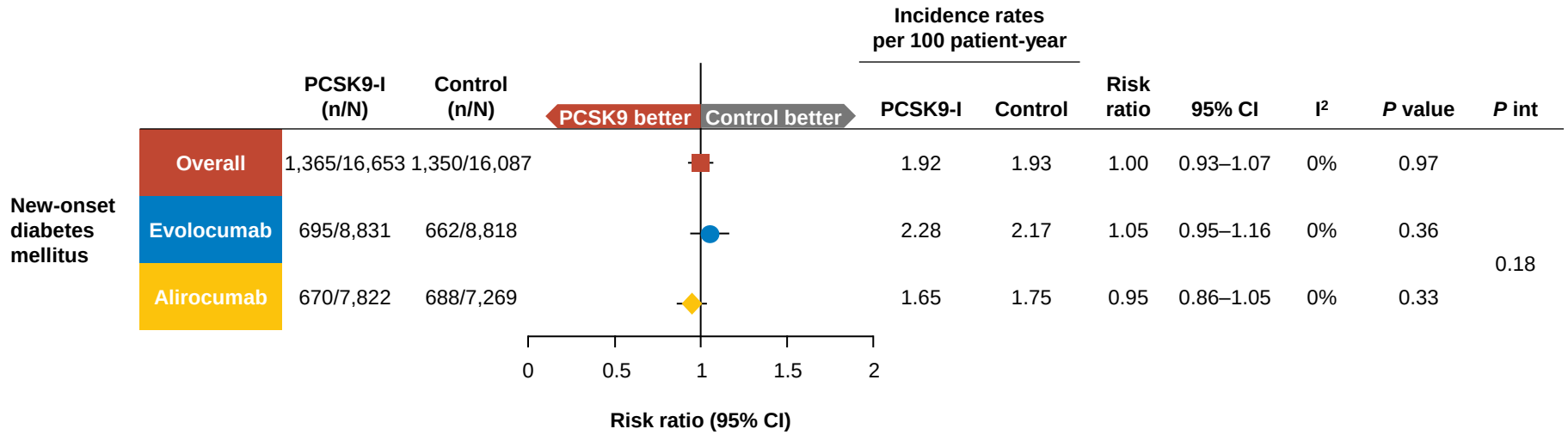
En metanálisis de ensayos clínicos con iPCSK9 tampocó se evidenció asociación entre estos fármacos y desarrollo de DM.

A meta-analysis of 39 RCTs comprising 66,478 patients examined the safety and efficacy of evolocumab or alirocumab vs placebo or other lipid-lowering therapies

Safety Endpoint for PCSK9 Inhibitors vs Control



There were no significant differences in the risk of NODM between PCSK9 inhibitors and controls

CI, confidence interval; NODM, new-onset diabetes mellitus; PCSK9, proprotein convertase subtilisin/kexin type 9; RCT, randomized controlled trial.

Guedeney P, et al. *Eur Heart J*. 2019;0:1-9.

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SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Benefits of Achieving Very Low LDL-C Levels With Pharmacologic Interventions

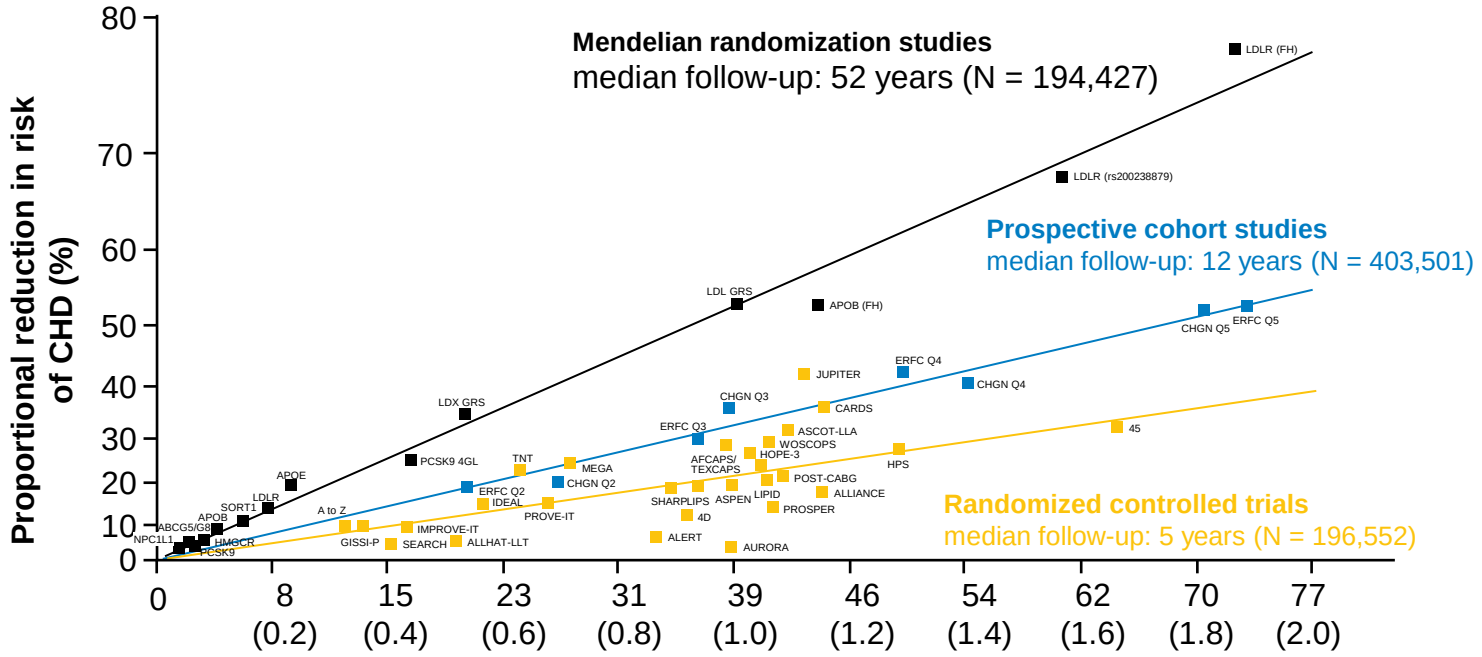
SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Las concentraciones plasmáticas de LDL se asocian con un incremento del riesgo cardiovascular, siendo ésto dosis-dependiente.

A meta-analysis of 49 studies demonstrated a consistent dose-dependent log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD

Reducing plasma LDL-C levels with a statin leads to dose-dependent reduction in the risk of major ASCVD events that is proportional to the absolute magnitude of the reduction in achieved LDL-C

Genetic Studies and Pharmacologically Lowered LDL-C Show a Causality With Reduced CHD Risk



See slide notes for trial acronyms.

ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

Ference BA, et al. *Eur Heart J*. 2017;38:2459-2472.

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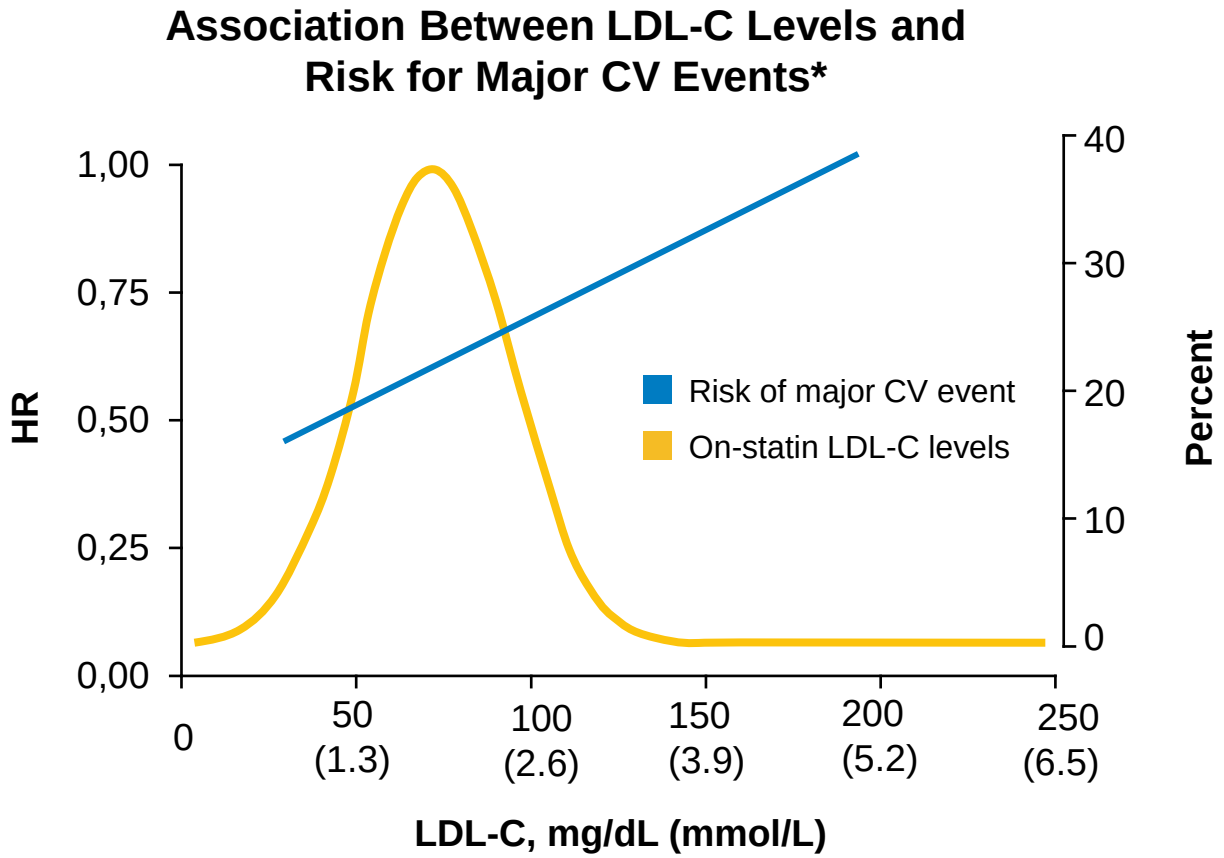
El riesgo de eventos cardiovasculares mayores se incrementa con el aumento en los valores de LDL.

A meta-analysis of 38,153 patients from eight randomized controlled trials evaluated the association between very low LDL-C levels achieved with statin therapy and CVD risk

Patients who achieve very low LDL-C levels (< 50 mg/dL [< 1.3 mmol/L]) have a lower risk for major CV events than those achieving moderately low levels (50–75 mg/dL [1.3–1.9 mmol/L] or 75–100 mg/dL [1.9–2.6 mmol/L])



*Distribution of achieved on-statin LDL-C levels (yellow curve; right y-axis) and the risk of major CV events (blue line; left y-axis); x-axis represents achieved on-statin LDL-C levels.

CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

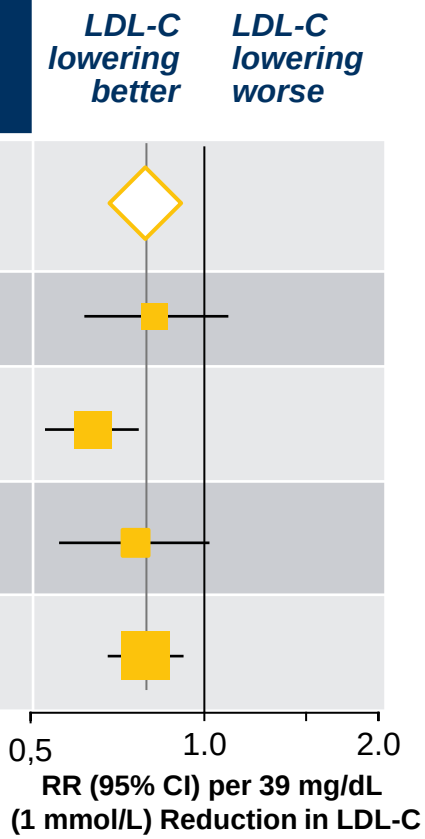
Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64:485-494.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

En metaanálisis reciente, se objetivó que valores de LDL muy bajos por debajo de 20 mg/dl reducen riesgo cardiovascular.

A meta-analysis of data from the CTTC, IMPROVE-IT, FOURIER, and REVEAL studies evaluated the safety and efficacy of further lowering of LDL-C levels in patients presenting with median LDL-C levels ≤ 70 mg/dL (≤ 1.8 mmol/L)

Outcome	Patients with events, no.		RR (95% CI)
	Experimental arm	Control arm	
Major vascular events	4,604	4,966	0.79 (0.70–0.88)
Coronary heart death	836	891	0.82 (0.62–1.10)
MI	1,671	1,930	0.64 (0.53–0.77)
Ischemic stroke	737	804	0.76 (0.56–1.02)
Coronary revascularization	3,003	3,228	0.79 (0.68–0.92)



Note: Ischemic stroke was used where available; otherwise all stroke was used. The size of the boxes is proportional to the number of events, and horizontal lines represent 95% CIs.

CI, confidence interval; CTTC, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; IMPROVE-IT, Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; REVEAL, Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification; RR, risk ratio.

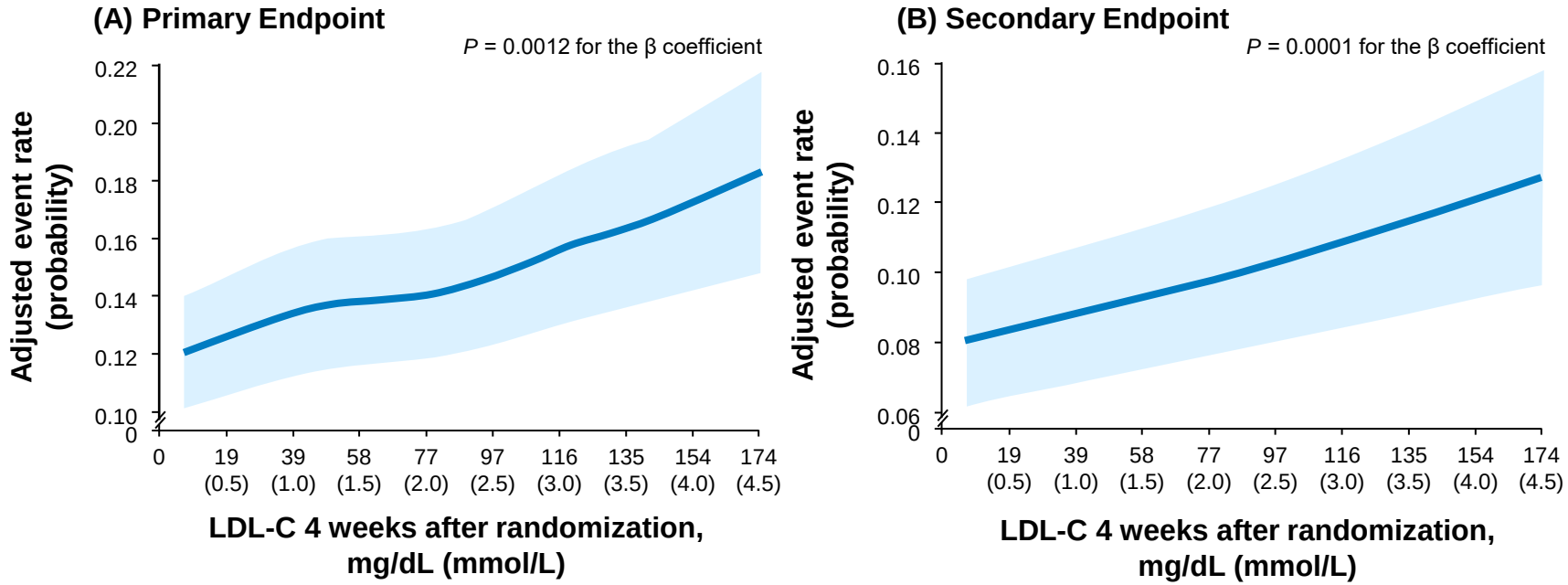
Sabatine MS, et al. *JAMA Cardiol*. 2018;3(9):823-828.

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

En estudio FOURIER, el riesgo de eventos cardiovasculares mayores se reduce conforme se logran cifras bajas de LDL.

A prespecified secondary analysis of 25,982 patients from the FOURIER trial explored the relationship between progressively lower LDL-C concentrations achieved at 4 weeks and subsequent CV outcomes

Relationship Between Achieved LDL-C Concentration at 4 Weeks and Risk of the (A) Primary and (B) Key Secondary Efficacy Endpoints*



The risk of the primary (composite of CV death, MI, stroke, coronary revascularization, or hospital admission for unstable angina) and secondary (composite of CV death, MI, and stroke) efficacy endpoints after week 4 was lower with decreasing achieved LDL-C concentration at week 4

*The blue line represents the adjusted probability of an event and blue areas are the 95% CIs of the regression model estimate.

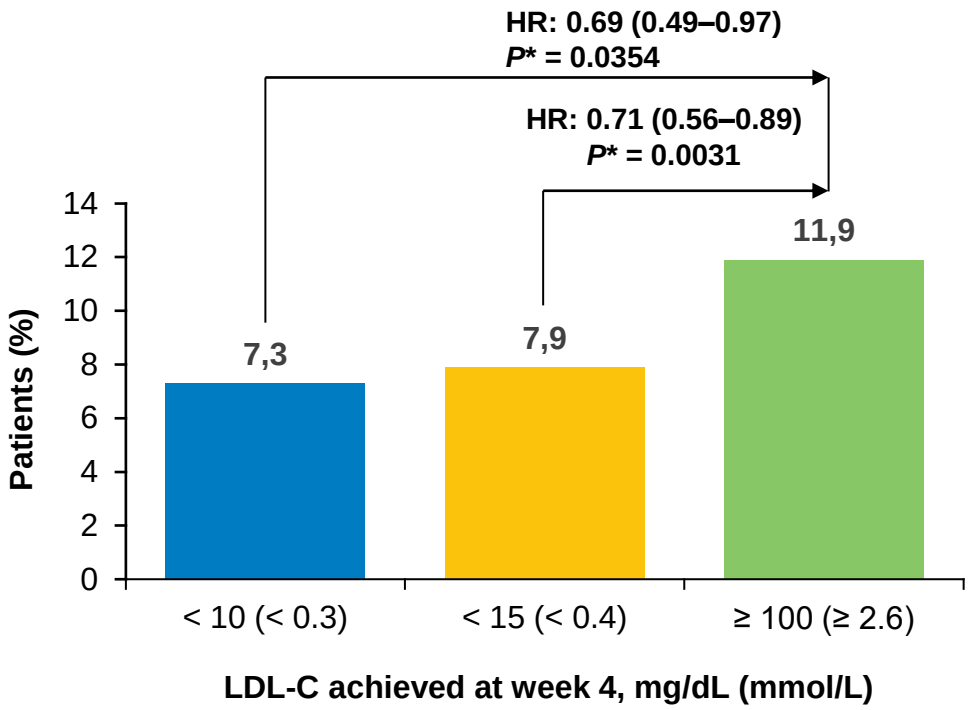
CI, confidence interval; CV, cardiovascular; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Giugliano RP, et al. *Lancet*. 2017;390:1962-1971.

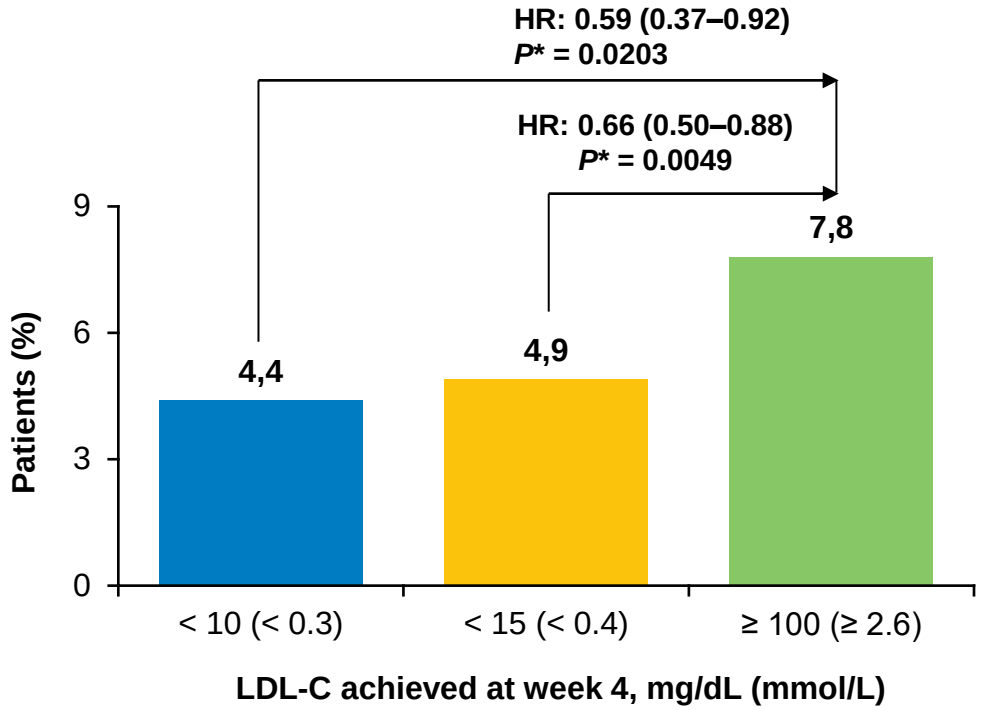
SOCIEDAD ASTURIANA DE CARDIOLOGÍA

Achievement of Ultra-low LDL-C Levels in FOURIER Further Reduced the Risk of Major CV Events

Primary Endpoint (Composite of CV Death, MI, Stroke, Coronary Revascularization, Hospitalization for UA)



Secondary endpoint (Composite of CV death, MI, Stroke)



Major CV events progressively declined with lower achieved LDL-C at week 4

*P value compared with the group achieving an LDL-C ≥ 100 mg/dL (≥ 2.6 mmol/L) at 4 weeks.

CV, cardiovascular; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; UA, unstable angina.

Giugliano RP, et al. *Lancet.* 2017;390:1962-1971.

Non-Amgen

SOCIEDAD ASTURIANA DE CARDIOLOGÍA

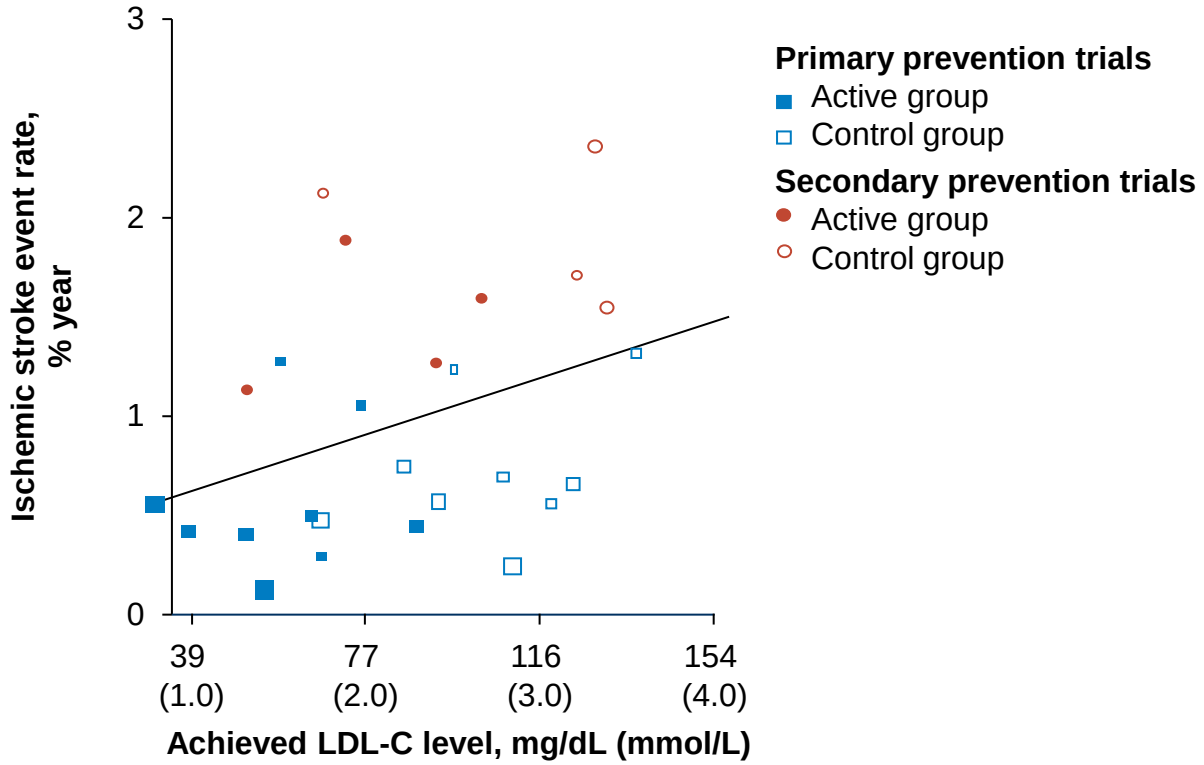
Además, cifras muy bajas de LDL se asocian con reducción en el riesgo de ictus isquémico.

A meta-analysis of 222,149 participants in 23 randomized trials evaluated the association between achieved LDL-C levels and stroke risk

Evaluated trials were categorized according to achieved LDL-C levels: < 50 mg/dL (< 1.3 mmol/L), 50–70 mg/dL (1.3–1.8 mmol/L), and > 70 mg/dL (> 1.8 mmol/L)

For ischemic stroke, each 39 mg/dL (1 mmol/L) decrease in LDL-C was associated with a risk reduction of 28.6% (95% CI: -0.019–0.591, *P* = 0.065)

Association Between Achieved LDL-C Level and Ischemic Stroke Event Rate*



*The size of each square on the graph indicates the weight of each trial, which was derived from the inverse of variance of the event rate of each trial.

CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

Shin J, et al. *Eur J Prev Cardiol*. 2019. Epub ahead of print.

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CONCLUSIONES

- **La enfermedad cardiovascular es una entidad de elevada prevalencia, morbilidad y mortalidad.; con un alto impacto económico y social.**

- **El objetivo de LDL por debajo de 55 en pacientes de muy alto riesgo cardiovascular es difícil de conseguir con tratamiento hipolipemiante convencional. Muchos de estos pacientes se encuentran infratratados.**

- **No se ha evidenciado relación directa entre niveles muy bajos de LDL y enfermedades neurológicas. Alto perfil de seguridad de estos fármacos también en desarrollo de diabetes.**

- **La reducción de cifras de LDL en valores absolutos se acompaña de reducción de riesgo relativo para desarrollo de eventos cardiovasculares mayores.**

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