1ère Année de Médecine

Cas de liaison

Athérosclérose #5

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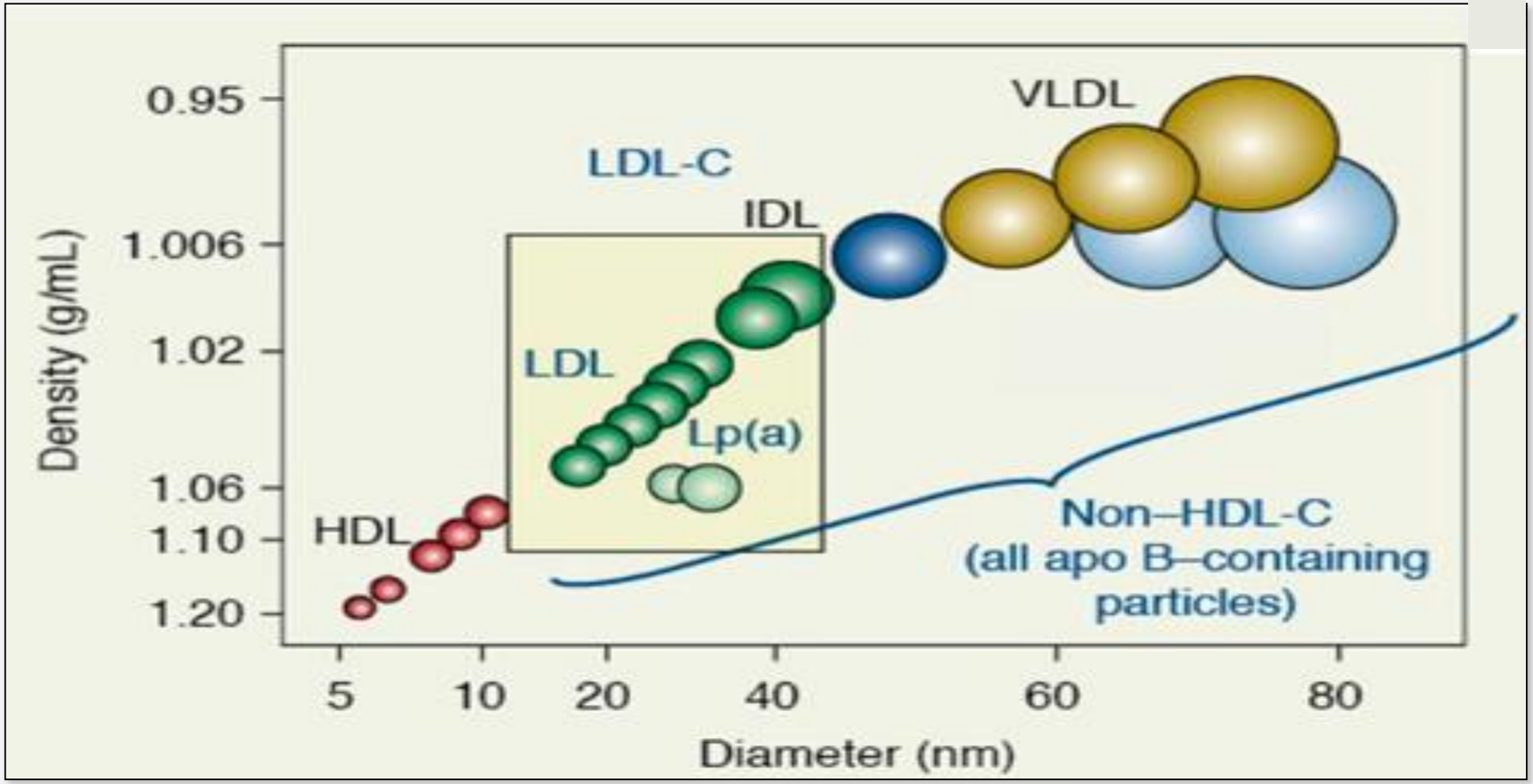
Genève, le 12 janvier 2026

Caractéristiques des lipoprotéines



LDL-Cholesterol

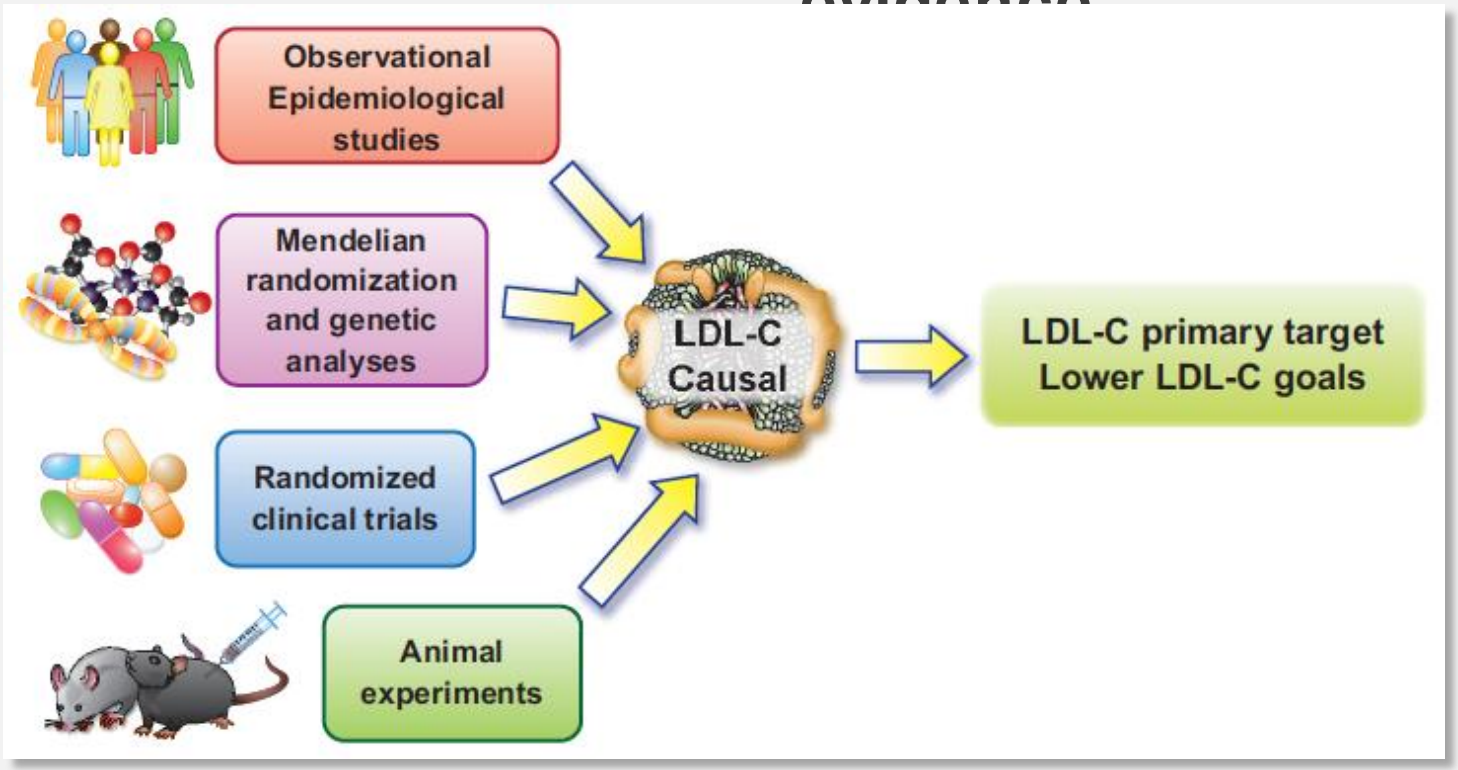
Clear relationship between LDL-C and risk of CV events

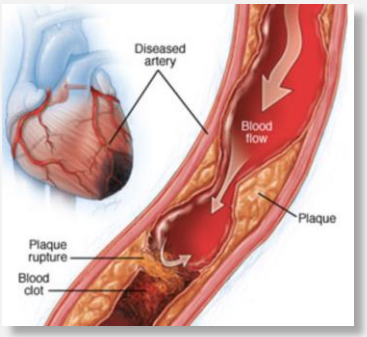
ESC European Society of Cardiology
European Heart Journal (2022) 43, 3198–3208
https://doi.org/10.1093/eurheartj/ehab841
STATE OF THE ART REVIEW
Dyslipidaemias

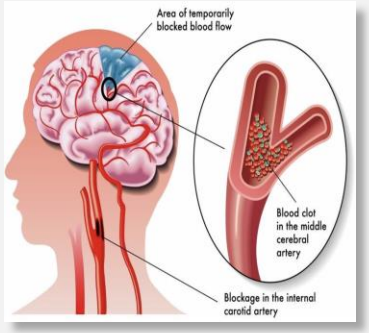
The dawn of a new era of targeted lipid-lowering therapies

Lale Tokgözoğlu[1] and Peter Libby [2]*

LDL-C is the main driver for atherosclerosis: 4 compelling lines of evidence

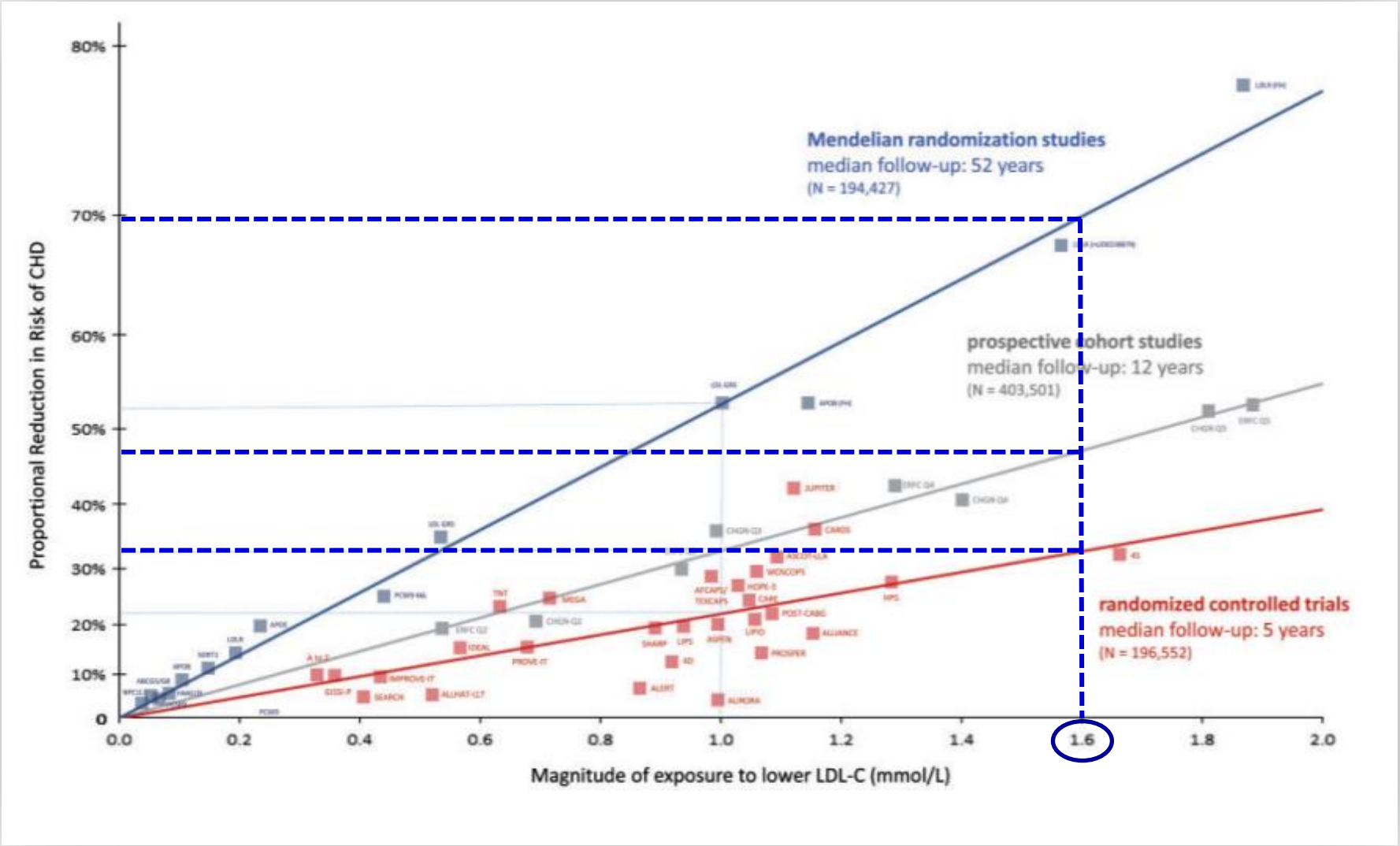






Eur Heart J 2022;43:3198

Time-Exposure to low LDL-C



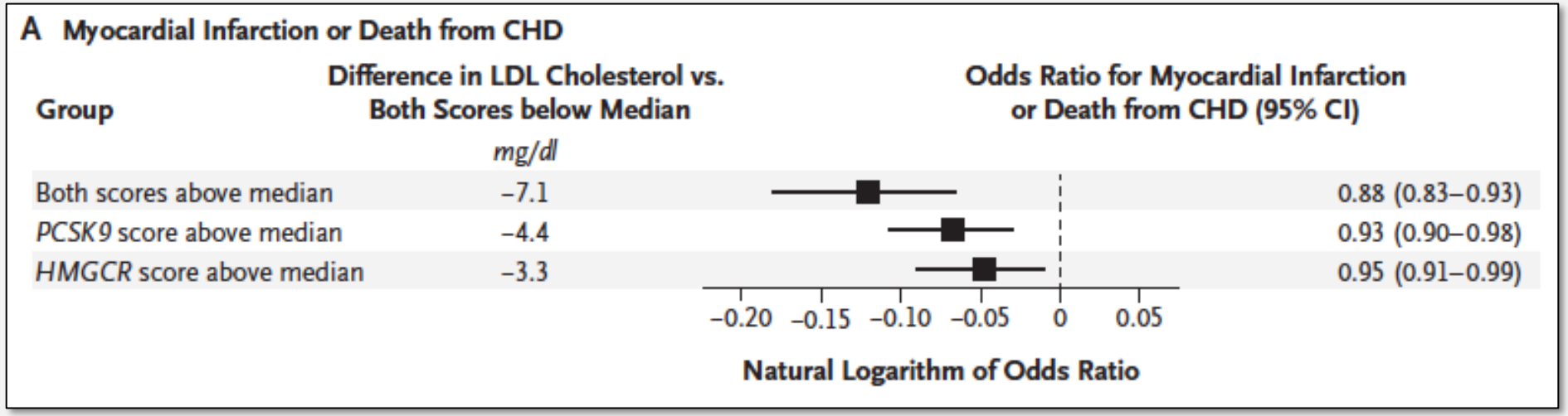
Eur Heart J 2017;38:2459

Reduced LDL-C via mutations is associated with low CVD in humans

ORIGINAL ARTICLE

Variation in *PCSK9* and *HMGCR* and Risk of Cardiovascular Disease and Diabetes

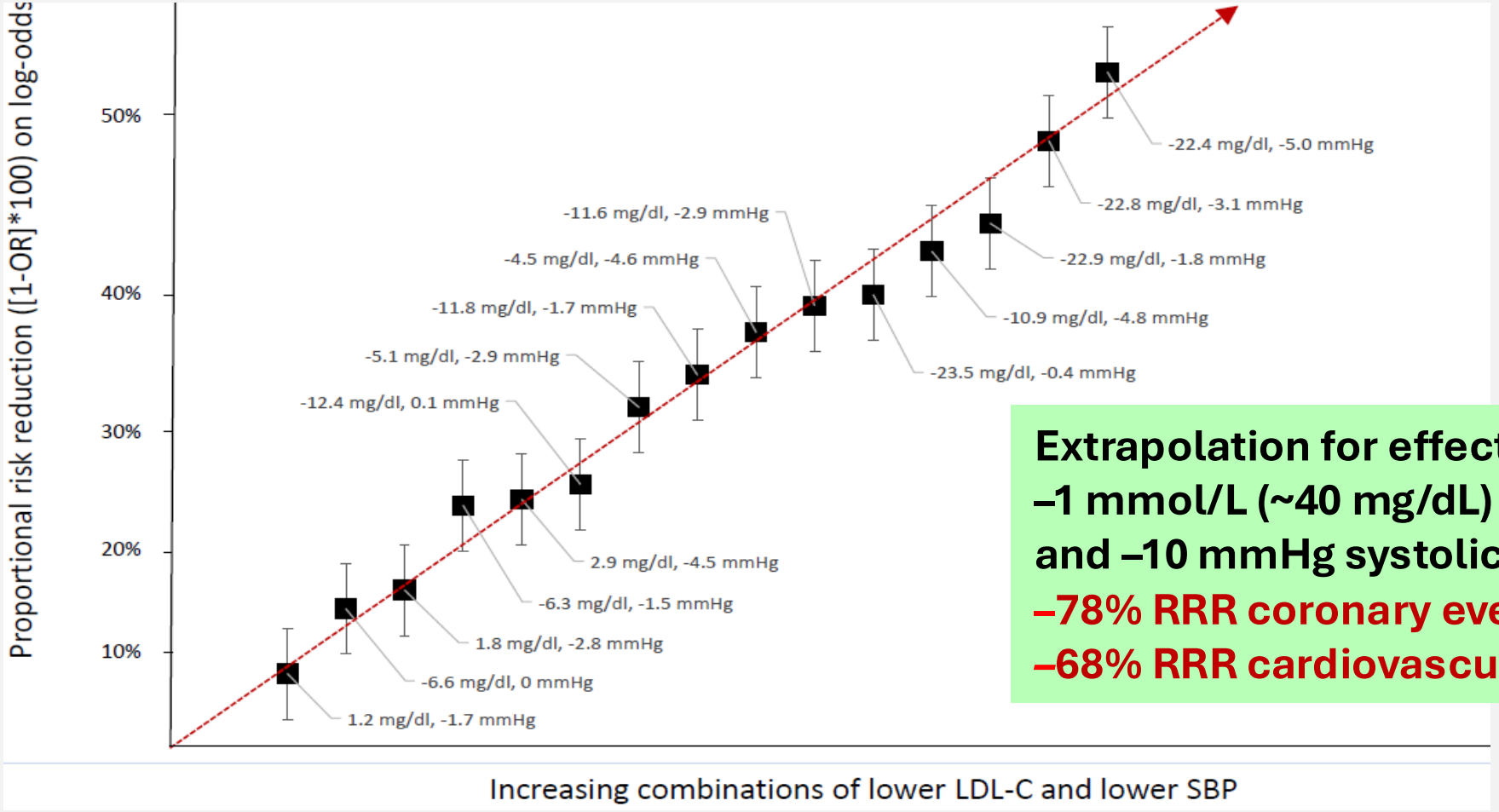
Brian A. Ference, M.D., Jennifer G. Robinson, M.D., M.P.H., Robert D. Brook, M.D., Alberico L. Catapano, Ph.D., M. John Chapman, Ph.D., David R. Neff, D.O., Szilard Voros, M.D., Robert P. Giugliano, M.D., George Davey Smith, M.D., D.Sc., Sergio Fazio, M.D., Ph.D., and Marc S. Sabatine, M.D., M.P.H.



N Engl J Med 2016;375:2144

Mendelian randomization: effects of lower LDL-C, lower SBP or both on risk of major cardiovascular events

N=438,952 (54.1% female, mean age 65.2 years); 24,980 CV events; quartile values of genetic scores



Extrapolation for effect of –1 mmol/L (~40 mg/dL) LDL-C and –10 mmHg systolic BP:

–78% RRR coronary events

–68% RRR cardiovascular deaths

JAMA 2019 Sep 2 doi: 10.1001/jama.2019.14120

Lipid levels during the first days of life

ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 7, Issue 4, 2014

ISSN - 0974-2441

Research Article

NEONATAL LIPID LEVELS – CAN THEY BE A BENCHMARK FOR LIPID LOWERING IN ADULTS?

SUDHARSHANA MURTHY KA[1], AMBARISHA BHANDIWAD[2], MURTHY KVKSN[3], SHIVANI AGGARWAL[4]

Table 3: Cord blood lipid parameters in present study and earlier evidence

Mean(mg/dl)	Pardo *et al*[16]	SV Esfarjani *et al*[17]	Schaefer Graf U M *et al*[18]	Rakhi Jain *et al*[19]	KARB s *et al*[20]	Present study
Total Cholesterol	70.42 ± 1.63	81.02 ± 19.75	63.5 ± 17.7	98.2 ± 34.9	73.64 ± 21.64	73.83 ± 15.83
HDL Cholesterol	26.75 ± 0.65	25.09 ± 7.34	-	29 ± 10.7	23.25 ± 7.66	21.13 ± 6.00
LDL Cholesterol	34.38 ± 1.29	48.92 ± 16.34	-	36.4 ± 20	41.81 ± 17.88	36.63 ± 12.82
Triglycerides	-	42 ± 29.10	41.6 ±21.8	118.5 ± 9	33.75 ± 16.39	49.38 ±23.81
VLDL Cholesterol	-	-	-	28.6 ± 17.5	12.8 ± 11.08	13.58 ± 16.83
TC/HDL	2.71± 0.06	2.33	-	3.52 ± 1.4	-	3.74 ± 1.25
LDL/HDL	-	-	-	1.41 ± 0.8	-	1.84 ± 0.82
RBS	-	-	85 ± 21.4	-	-	38.78 ± 14.31
HbA1c	-	-	-	-	-	2%

En moyenne 1.2 -1.4 mmol/L

Asian J Pharm Clin Res 2014;4:165

What is the ideal level of LDL-cholesterol ?




0% heart attack

An ideal level of LDL-cholesterol should be between 40-80 mg/dL

1.2 – 1.8 mmol/L

MAGAZINE D'AOÛT 2016
DE LA CAISSE MALADIE CSS

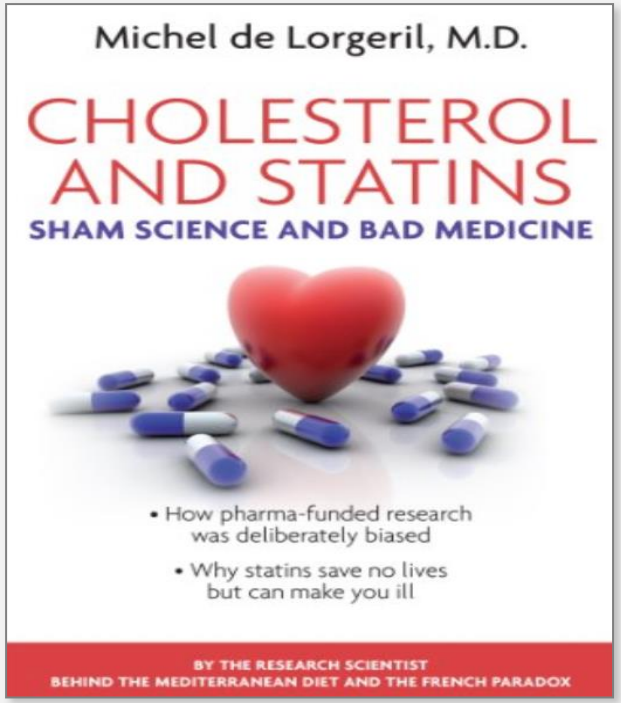
CSS MAGAZINE DOSSIER

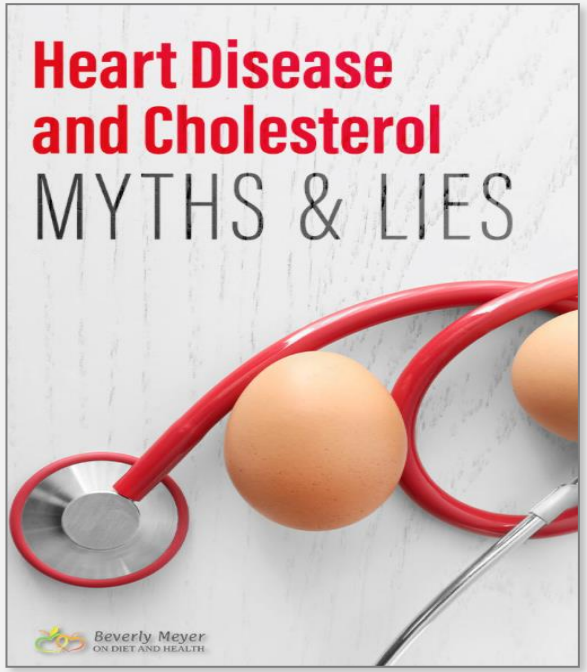
Et si le cholestérol n'était pas dangereux?

Le cholestérol a longtemps été considéré comme nocif. Aujourd'hui, ces craintes se dissipent, car cette substance lipoïdique assume des fonctions essentielles dans l'organisme.

Texte: Vera Sohmer

On parle souvent de «bon» cholestérol pour le premier et de «mauvais» pour le second. Le docteur Imoberdorf ne partage pas cette classification. Il est en effet d'avis que les deux formes de cholestérol accomplissent une mission importante. D'après lui, les personnes en bonne santé n'ont pas à re-

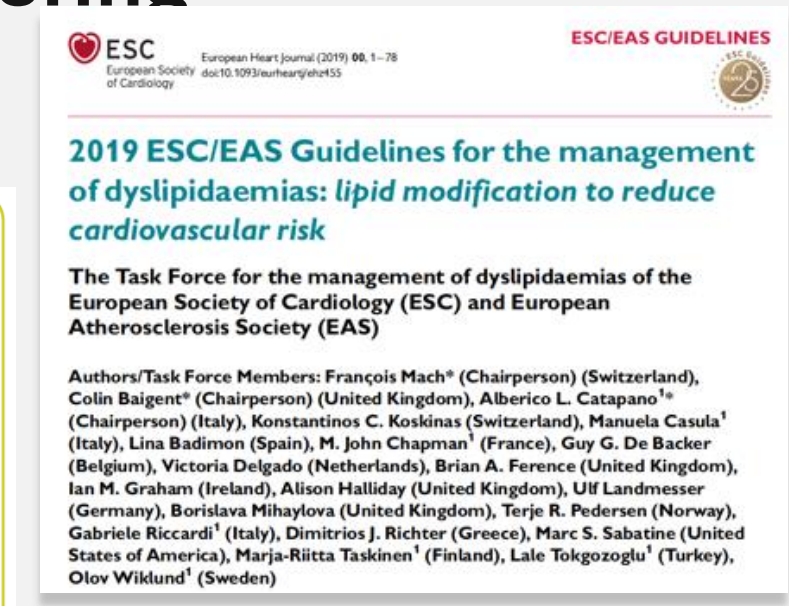


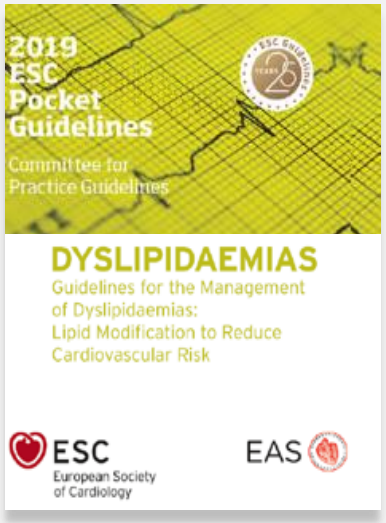


Intensity of pharmacological LDL-C lowering

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%





Eur Heart J 2020;41:111

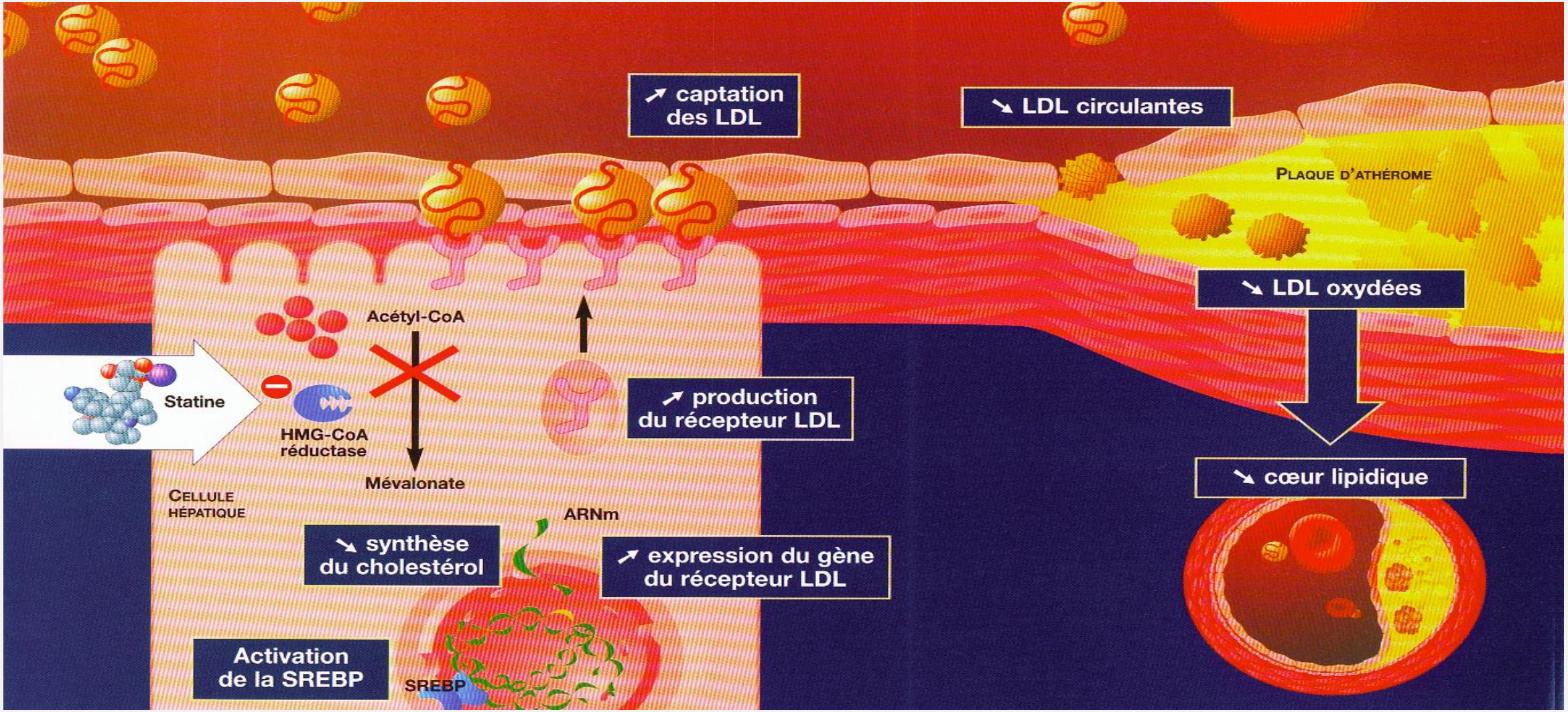
Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals[c] set for the specific level of risk.	I	A

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Statines & Cholestérol

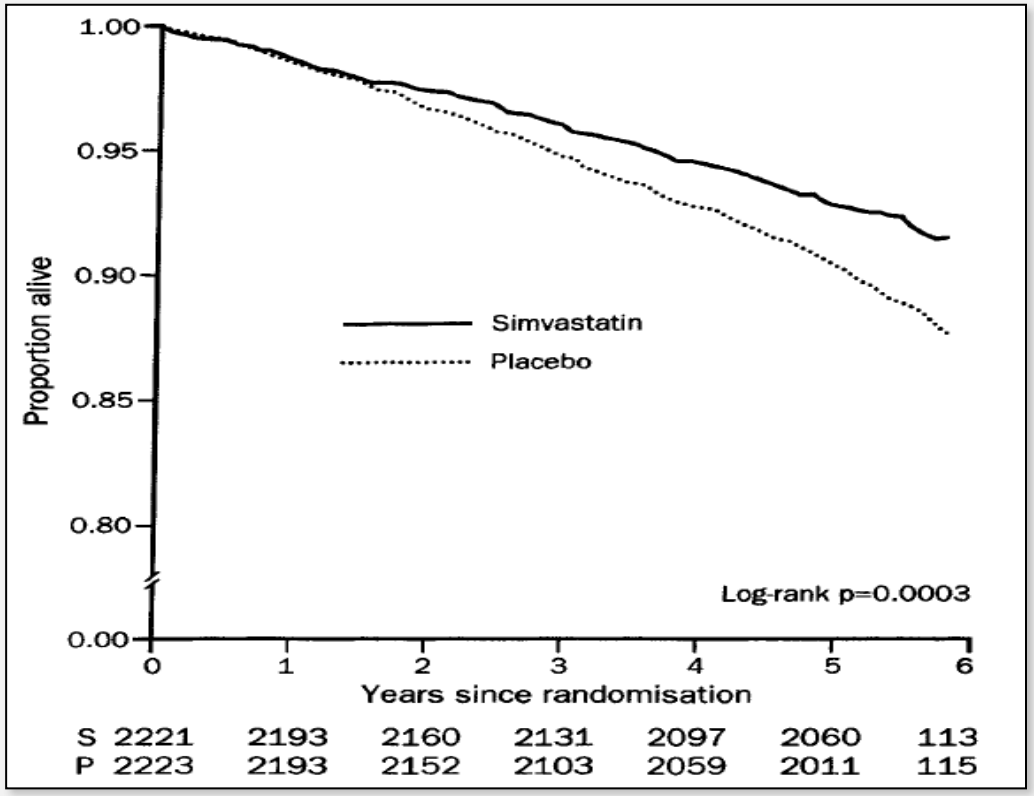


Statins – The evidences

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)

*Scandinavian Simvastatin Survival Study Group**

Lancet 1994;344:1383



RRR was 0.70 (95% CI 0.58-0.85, p=0.0003)

LDL-C went from 4.87 mmol/L to 3.17 mmol/L with simvastatin 20mg/d

Statins – The evidences

Early Statin Treatment Following Acute Myocardial Infarction and 1-Year Survival

Context Randomized trials have established statin treatment as secondary prevention in coronary artery disease, but it is unclear whether early treatment with statins following acute myocardial infarction (AMI) influences survival.

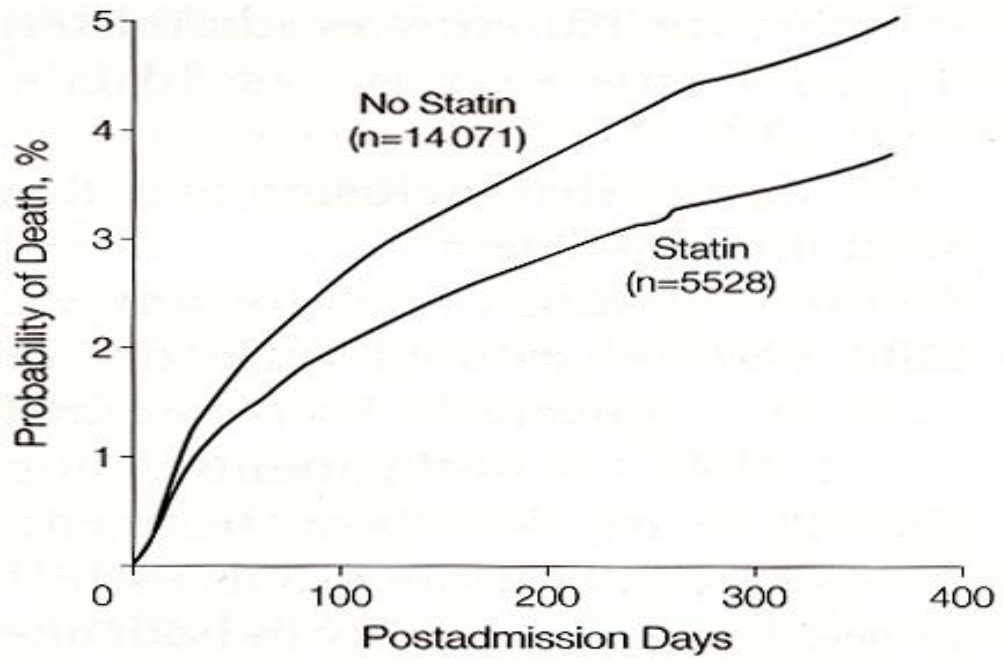
Objective To evaluate the association between statin treatment initiated before or at the time of hospital discharge and 1-year mortality after AMI.

Design and Setting Prospective cohort study using data from the Swedish Register of Cardiac Intensive Care on patients admitted to the coronary care units of 58 Swedish hospitals in 1995-1998. One-year mortality data were obtained from the Swedish National Cause of Death Register.

Patients Patients with first registry-recorded AMI who were younger than 80 years and who were discharged alive from the hospital, including 5528 who received statins at or before discharge and 14071 who did not.

JAMA 2001;285:430

Figure. Adjusted Probability of Mortality by Statin Treatment



Data were calculated using multiple Cox regression analysis (relative risk, 0.75; 95% confidence interval, 0.63-0.89; $P=.001$).

Statins save lives after acute MI

Statins – The evidences

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 8, 2004 VOL. 350 NO. 15

Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

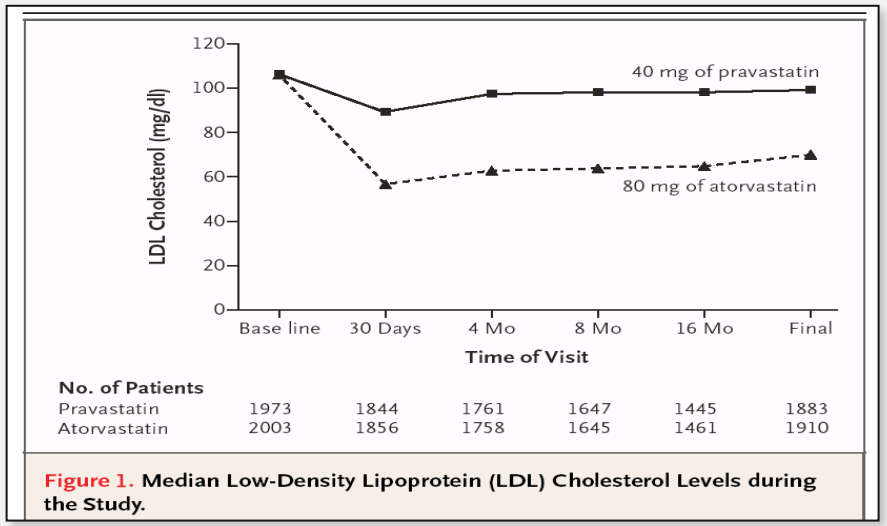
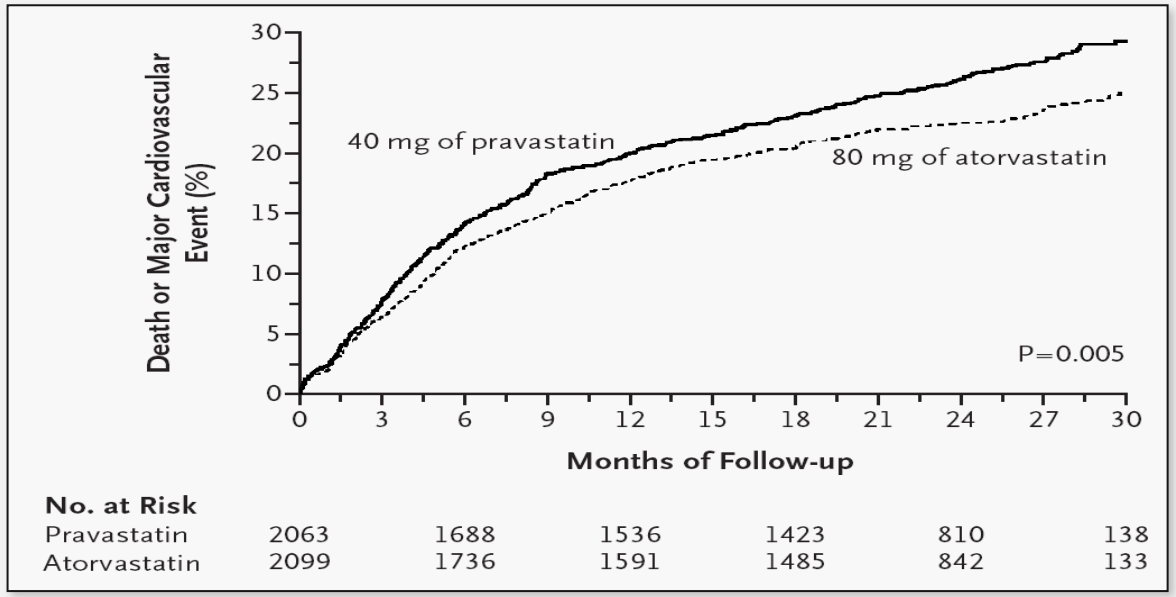


Figure 1. Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study.

→ 2.6 mmol/L

→ 1.8 mmol/L



N Engl J Med 2005;352:20

Statin – lipid-lowering & CV events

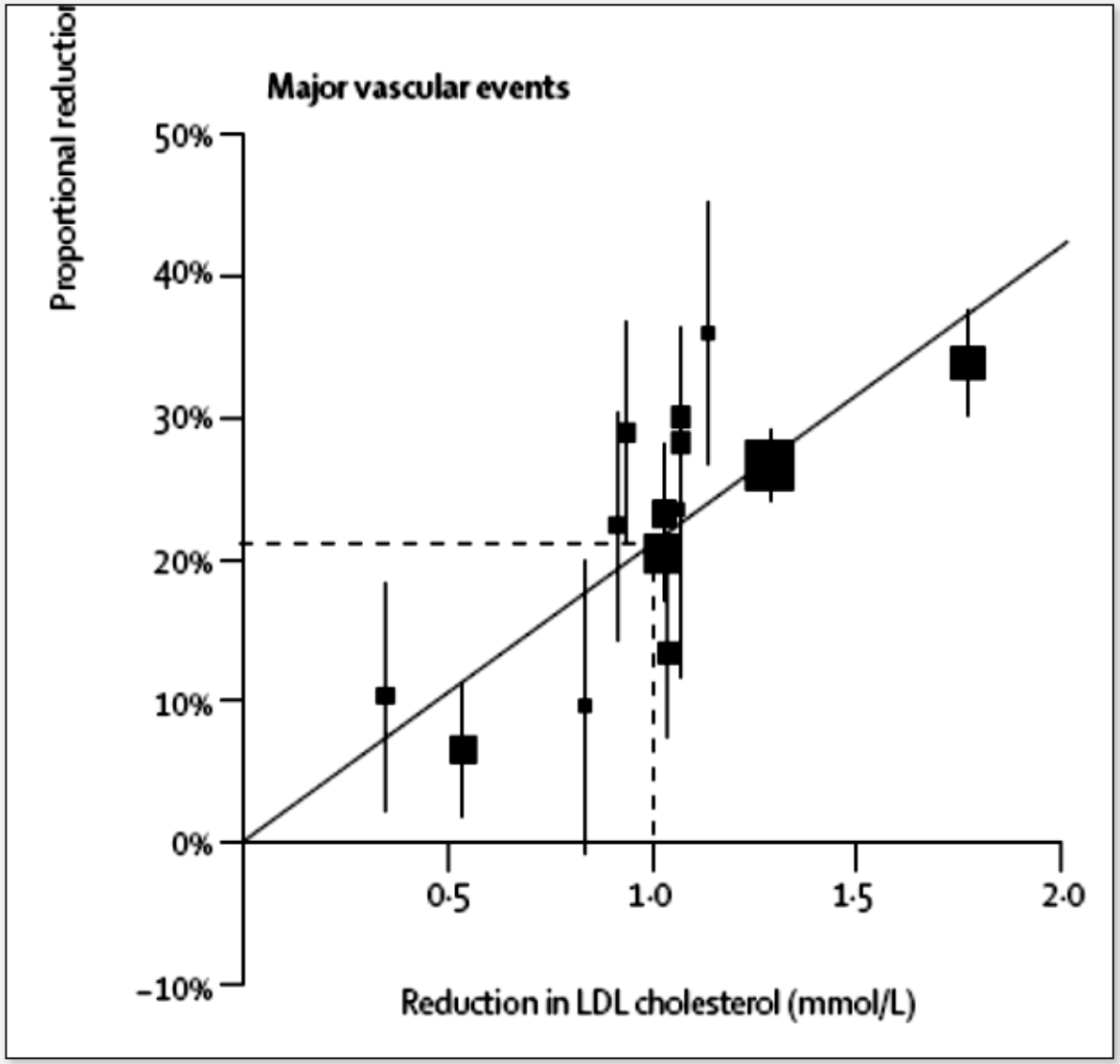
“The Lower is better”

- CTT-Analyse Lancet 2005,
  90’000 Patients, 14 Trials,
  Statin vs. Placebo:

  -> 1mmol/l LDL-C↓ ⇒ 21% RR↓

- CTT-Analyse Lancet 2010,
  170’000 Patients, 26 Trials;
  Statin vs Placebo +
  intensive vs. standard statin

  -> 1mmol/l LDL-C↓ ⇒ 28 RR↓

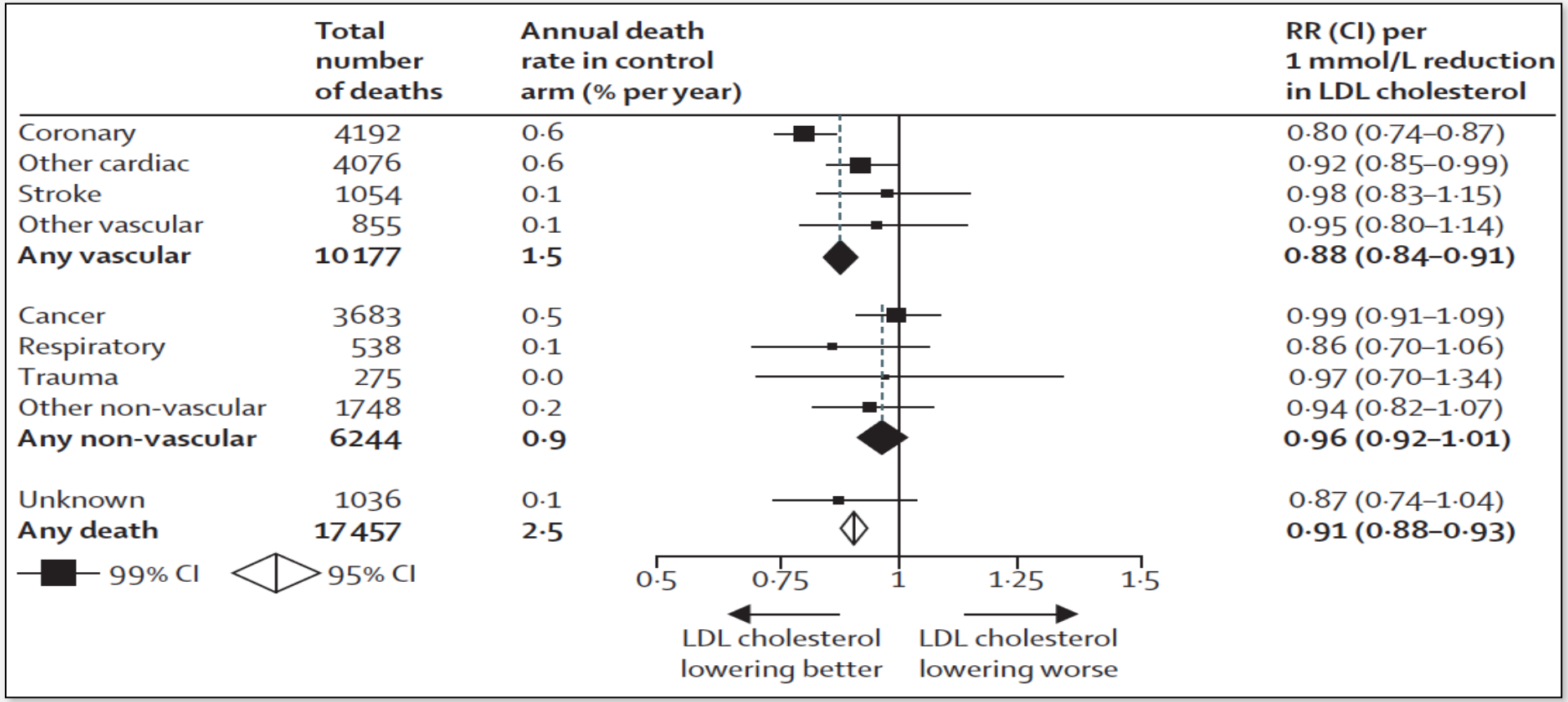


Cholesterol Treatment Trialists’ (CTT) Collaboration *Lancet* 2010;376:1670

Statins - The evidences

Interpretation of the evidence for the efficacy and safety of statin therapy

Rory Collins, Christina Reith, Jonathan Emberson, Jane Armitage, Colin Baigent, Lisa Blackwell, Roger Blumenthal, John Danesh, George Davey Smith, David DeMets, Stephen Evans, Malcolm Law, Stephen MacMahon, Seth Martin, Bruce Neal, Neil Poulter, David Preiss, Paul Ridker, Ian Roberts, Anthony Rodgers, Peter Sandercock, Kenneth Schulz, Peter Sever, John Simes, Liam Smeeth, Nicholas Wald, Salim Yusuf, Richard Peto



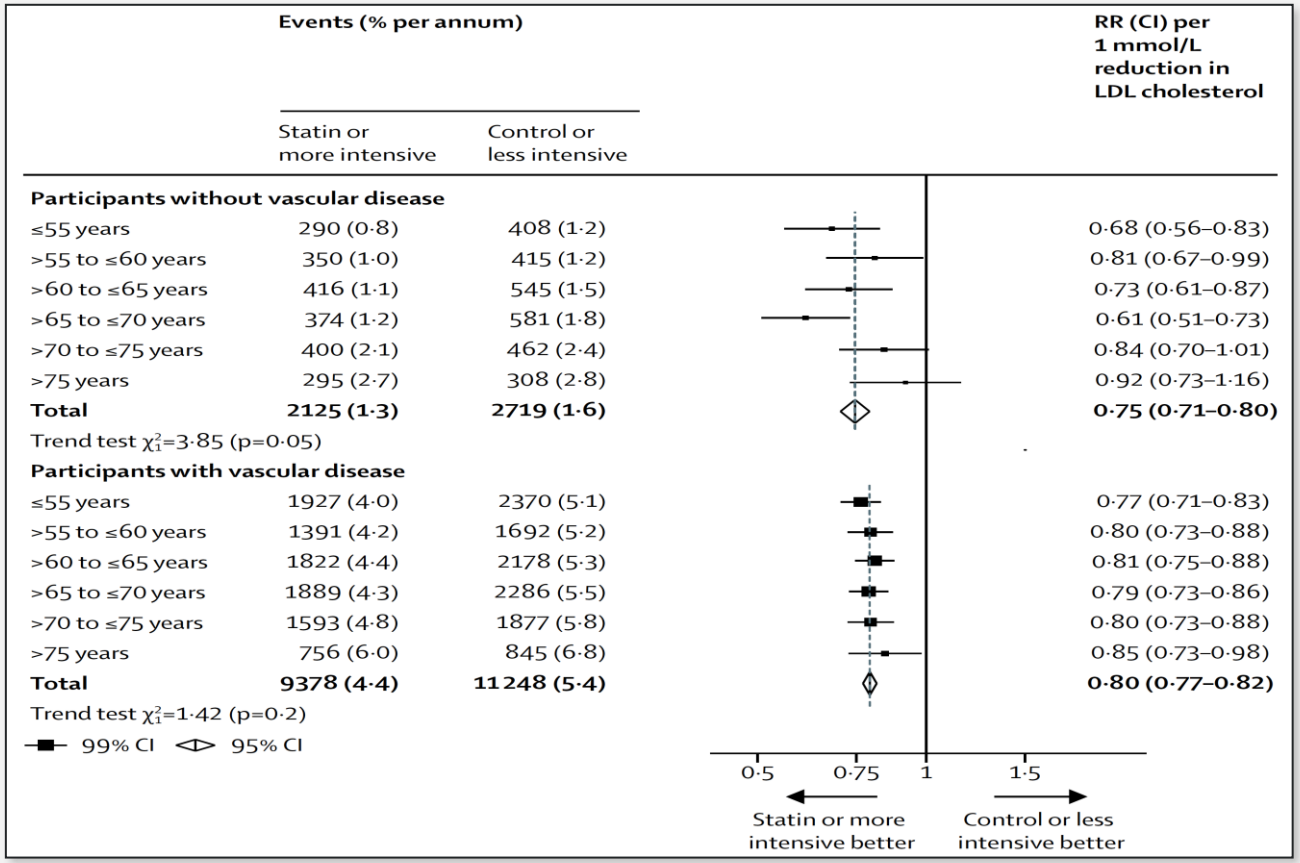
The Lancet 2016;388:2532

Statins - The evidence

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

*Cholesterol Treatment Trialists' Collaboration**

Lancet February 2nd, 2019

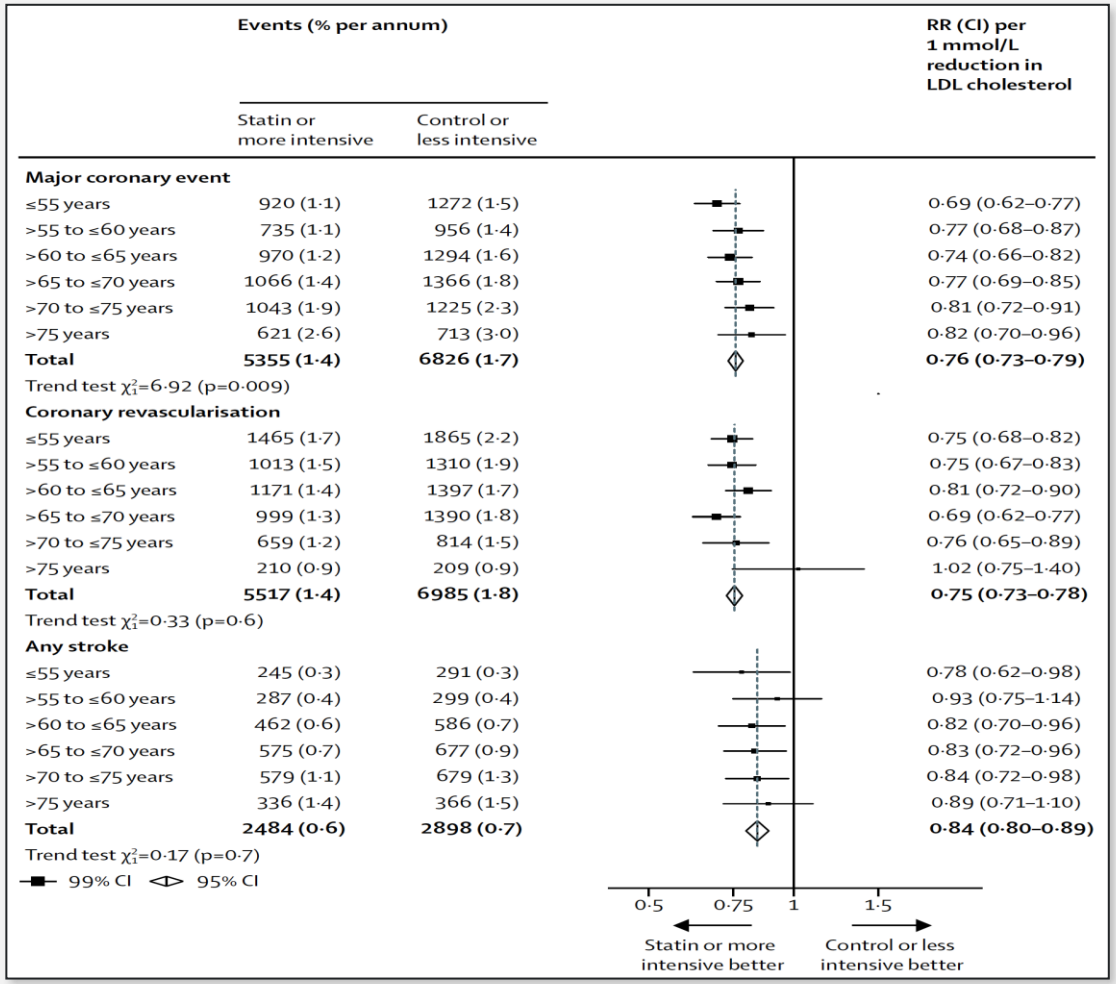


	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL cholesterol
	Statin or more intensive	Control or less intensive	
Participants without vascular disease			
≤55 years	290 (0·8)	408 (1·2)	0·68 (0·56–0·83)
>55 to ≤60 years	350 (1·0)	415 (1·2)	0·81 (0·67–0·99)
>60 to ≤65 years	416 (1·1)	545 (1·5)	0·73 (0·61–0·87)
>65 to ≤70 years	374 (1·2)	581 (1·8)	0·61 (0·51–0·73)
>70 to ≤75 years	400 (2·1)	462 (2·4)	0·84 (0·70–1·01)
>75 years	295 (2·7)	308 (2·8)	0·92 (0·73–1·16)
Total	**2125 (1·3)**	**2719 (1·6)**	**0·75 (0·71–0·80)**
Trend test χ^2_1=3·85 (p=0·05)			
Participants with vascular disease			
≤55 years	1927 (4·0)	2370 (5·1)	0·77 (0·71–0·83)
>55 to ≤60 years	1391 (4·2)	1692 (5·2)	0·80 (0·73–0·88)
>60 to ≤65 years	1822 (4·4)	2178 (5·3)	0·81 (0·75–0·88)
>65 to ≤70 years	1889 (4·3)	2286 (5·5)	0·79 (0·73–0·86)
>70 to ≤75 years	1593 (4·8)	1877 (5·8)	0·80 (0·73–0·88)
>75 years	756 (6·0)	845 (6·8)	0·85 (0·73–0·98)
Total	**9378 (4·4)**	**11248 (5·4)**	**0·80 (0·77–0·82)**
Trend test χ^2_1=1·42 (p=0·2)			

99% CI 95% CI

0·5 0·75 1 1·5

Statin or more intensive better | Control or less intensive better



	Events (% per annum)		RR (CI) per 1 mmol/L reduction in LDL cholesterol
	Statin or more intensive	Control or less intensive	
Major coronary event			
≤55 years	920 (1·1)	1272 (1·5)	0·69 (0·62–0·77)
>55 to ≤60 years	735 (1·1)	956 (1·4)	0·77 (0·68–0·87)
>60 to ≤65 years	970 (1·2)	1294 (1·6)	0·74 (0·66–0·82)
>65 to ≤70 years	1066 (1·4)	1366 (1·8)	0·77 (0·69–0·85)
>70 to ≤75 years	1043 (1·9)	1225 (2·3)	0·81 (0·72–0·91)
>75 years	621 (2·6)	713 (3·0)	0·82 (0·70–0·96)
Total	**5355 (1·4)**	**6826 (1·7)**	**0·76 (0·73–0·79)**
Trend test χ^2_1=6·92 (p=0·009)			
Coronary revascularisation			
≤55 years	1465 (1·7)	1865 (2·2)	0·75 (0·68–0·82)
>55 to ≤60 years	1013 (1·5)	1310 (1·9)	0·75 (0·67–0·83)
>60 to ≤65 years	1171 (1·4)	1397 (1·7)	0·81 (0·72–0·90)
>65 to ≤70 years	999 (1·3)	1390 (1·8)	0·69 (0·62–0·77)
>70 to ≤75 years	659 (1·2)	814 (1·5)	0·76 (0·65–0·89)
>75 years	210 (0·9)	209 (0·9)	1·02 (0·75–1·40)
Total	**5517 (1·4)**	**6985 (1·8)**	**0·75 (0·73–0·78)**
Trend test χ^2_1=0·33 (p=0·6)			
Any stroke			
≤55 years	245 (0·3)	291 (0·3)	0·78 (0·62–0·98)
>55 to ≤60 years	287 (0·4)	299 (0·4)	0·93 (0·75–1·14)
>60 to ≤65 years	462 (0·6)	586 (0·7)	0·82 (0·70–0·96)
>65 to ≤70 years	575 (0·7)	677 (0·9)	0·83 (0·72–0·96)
>70 to ≤75 years	579 (1·1)	679 (1·3)	0·84 (0·72–0·98)
>75 years	336 (1·4)	366 (1·5)	0·89 (0·71–1·10)
Total	**2484 (0·6)**	**2898 (0·7)**	**0·84 (0·80–0·89)**
Trend test χ^2_1=0·17 (p=0·7)			

99% CI 95% CI

0·5 0·75 1 1·5

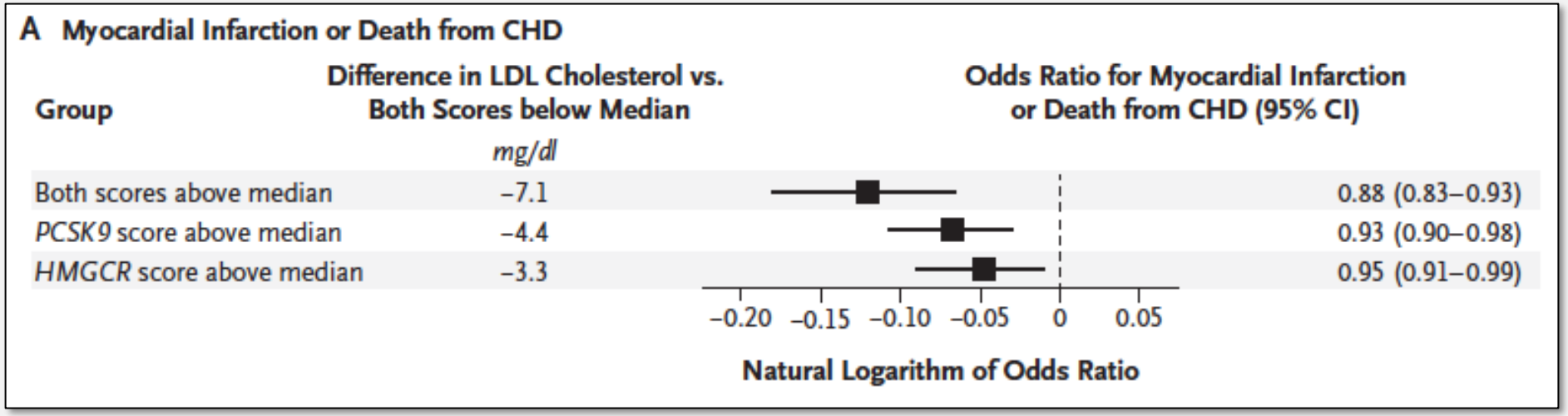
Statin or more intensive better | Control or less intensive better

Reduced LDL-C via mutations is associated with low CVD in humans

ORIGINAL ARTICLE

Variation in *PCSK9* and *HMGCR* and Risk of Cardiovascular Disease and Diabetes

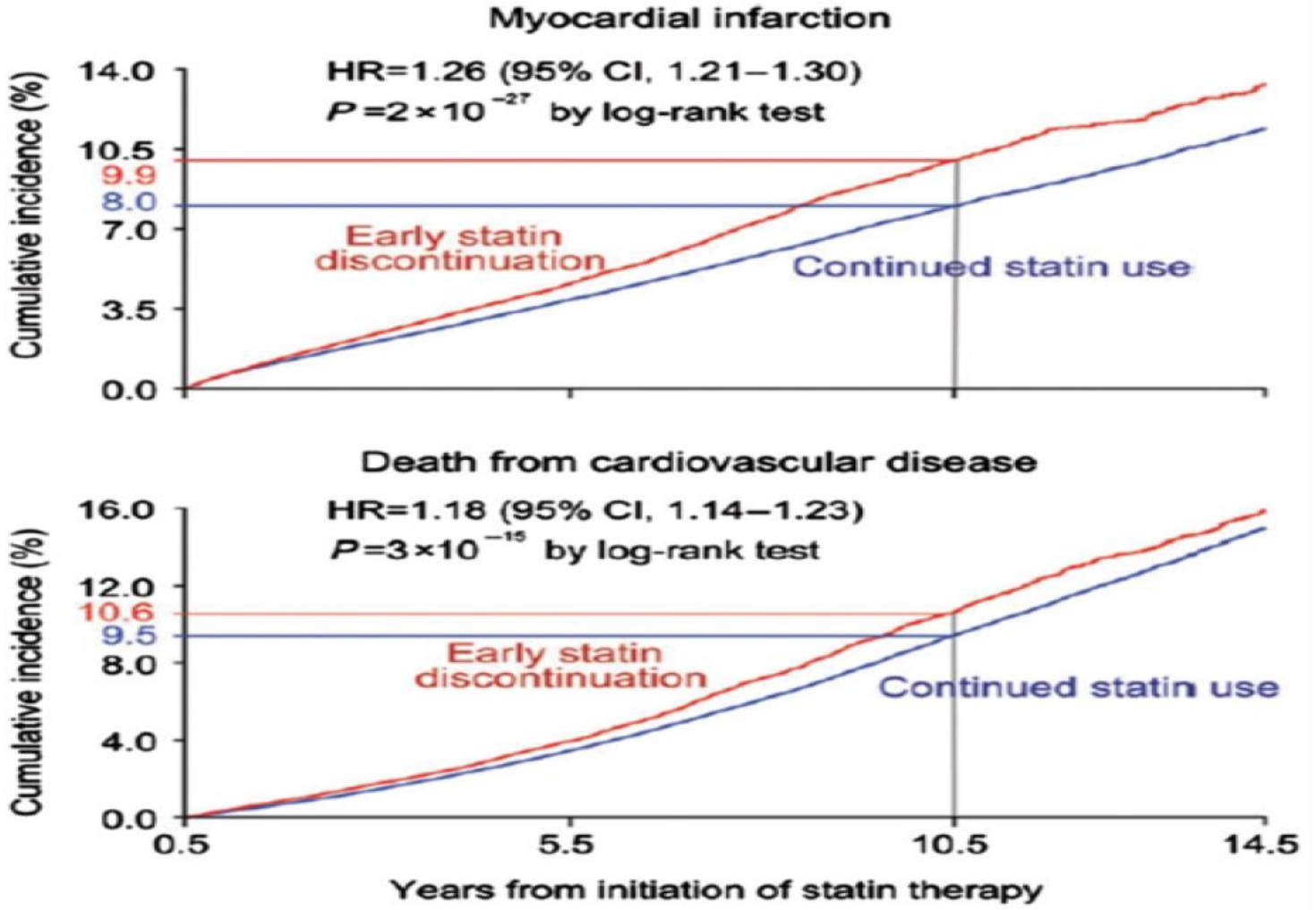
Brian A. Ference, M.D., Jennifer G. Robinson, M.D., M.P.H., Robert D. Brook, M.D., Alberico L. Catapano, Ph.D., M. John Chapman, Ph.D., David R. Neff, D.O., Szilard Voros, M.D., Robert P. Giugliano, M.D., George Davey Smith, M.D., D.Sc., Sergio Fazio, M.D., Ph.D., and Marc S. Sabatine, M.D., M.P.H.



N Engl J Med 2016;375:2144

The anti-statin lobby strikes again: time to set the record straight: Consequences of stopping statins

ESC European Society of Cardiology



Individuals	No. of statin users at risk			
Early statin discontinuation	84 800	26 865	4534	828
Continued statin use	424 000	147 083	31 735	6465

Eur Heart J 2018;39:335

ESC European Society of Cardiology
European Heart Journal (2018) 0, 1–18
doi:10.1093/eurheartj/ehy182

REVIEW

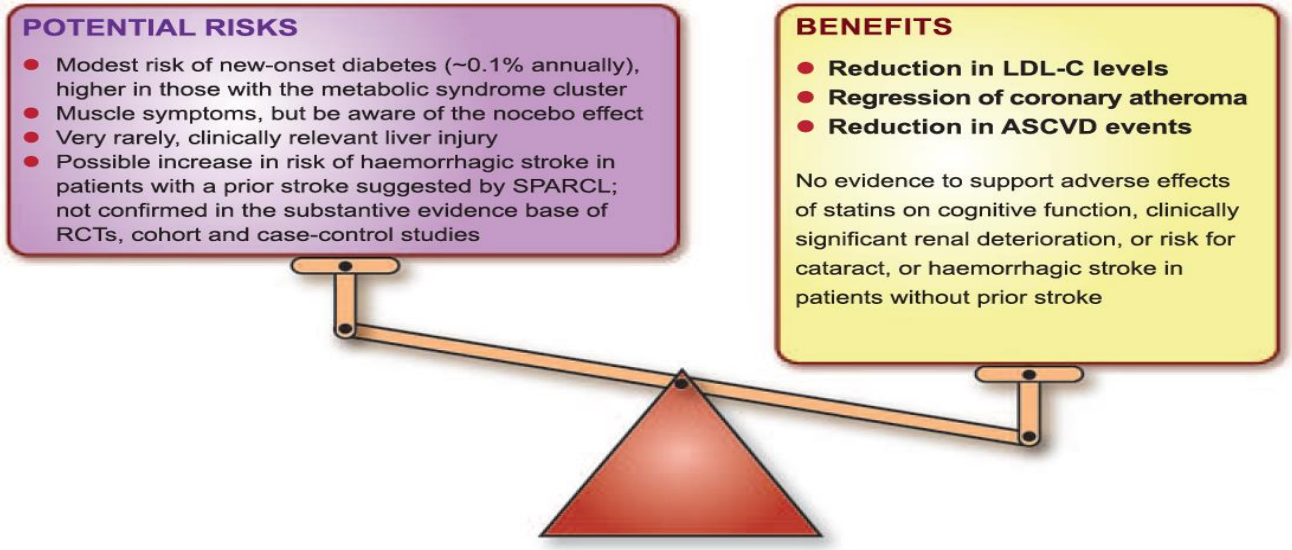
Clinical update

Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract

François Mach[1]*, Kausik K. Ray[2], Olov Wiklund[3,4], Alberto Corsini[5], Alberico L. Catapano[5], Eric Bruckert[6], Guy De Backer[7], Robert A. Hegele[8], G. Kees Hovingh[9], Terry A. Jacobson[10], Ronald M. Krauss[11], Ulrich Laufs[12], Lawrence A. Leiter[13], Winfried März[14,15], [16,17,18] Frederick J. Raal[19], Michael Roden[20,21], [F] Erik S. Stroes[9], Paul D. Thompson[25], [Lal] Baris Gencer[1], Jane K. Stock[28], Henry N[...] European Atherosclerosis Society Conse[...]

Eur Heart J 2018;39:2526

Highly favourable Benefit / Risk Ratio for statin therapy



Take home figure The cardiovascular benefit of long-term statin therapy far outweighs potential risks. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

Perception vs evidence – The nosebo effect

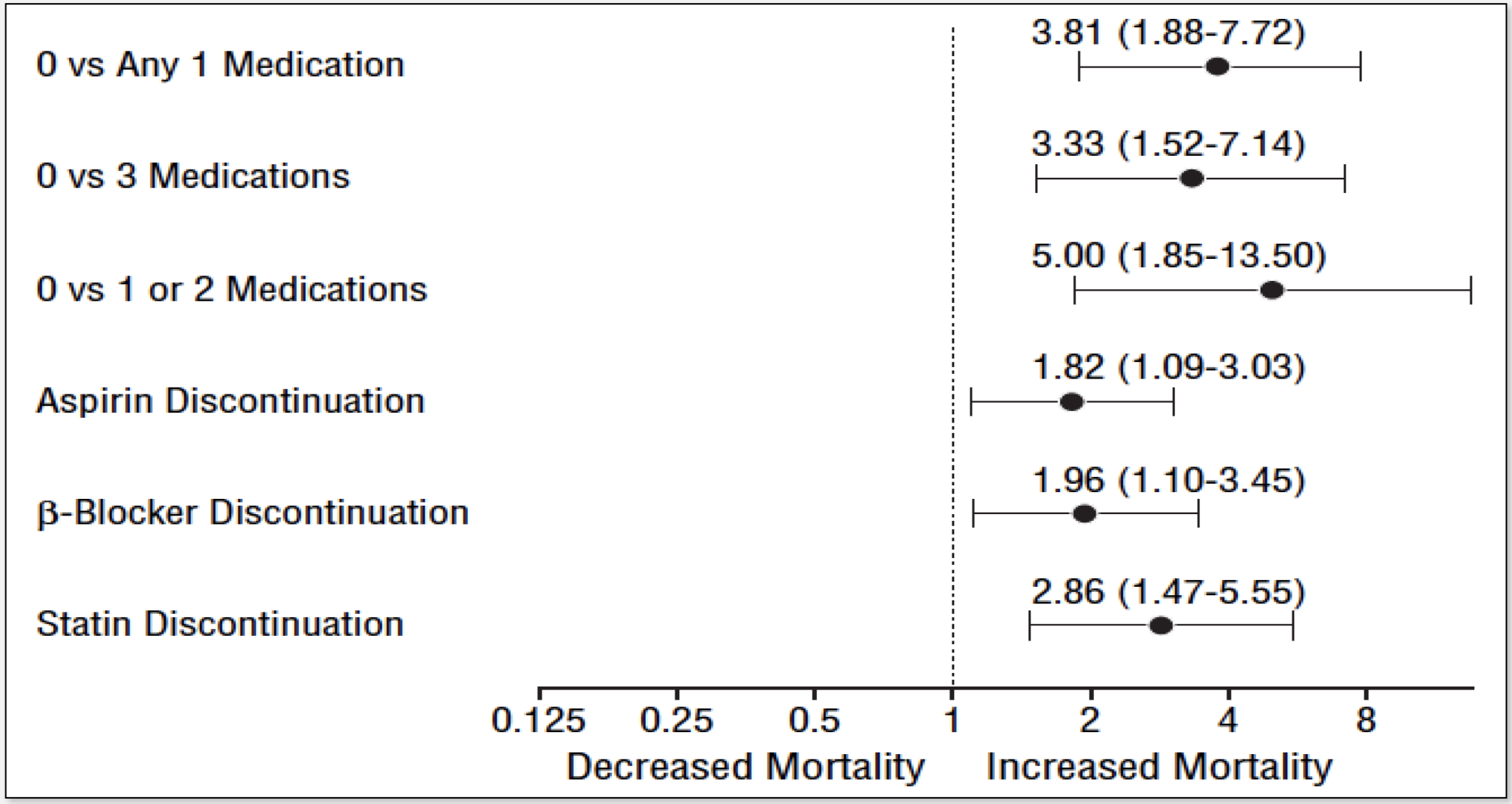
Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

Ajay Gupta, David Thompson, Andrew Whitehouse, Tim Collier, Bjorn Dahlof, Neil Poulter, Rory Collins, Peter Sever, on behalf of the ASCOT Investigators

	Blinded randomised phase (ASCOT-LLA)		Non-blinded non-randomised phase	
	Placebo (n=5079)	Atorvastatin (n=5101)	Atorvastatin non-user (n=3490)	Atorvastatin user (n=6409)
Muscle related				
Patients (n)	283	298	124	161
AE rate (% per annum)	2·00%	2·03%	1·00%	1·26%
HR (95% CI)	1	1·03 (0·88–1·21)	1	1·41 (1·10–1·79)
p value	..	0·72	..	0·006

Lancet 2017;389:2473

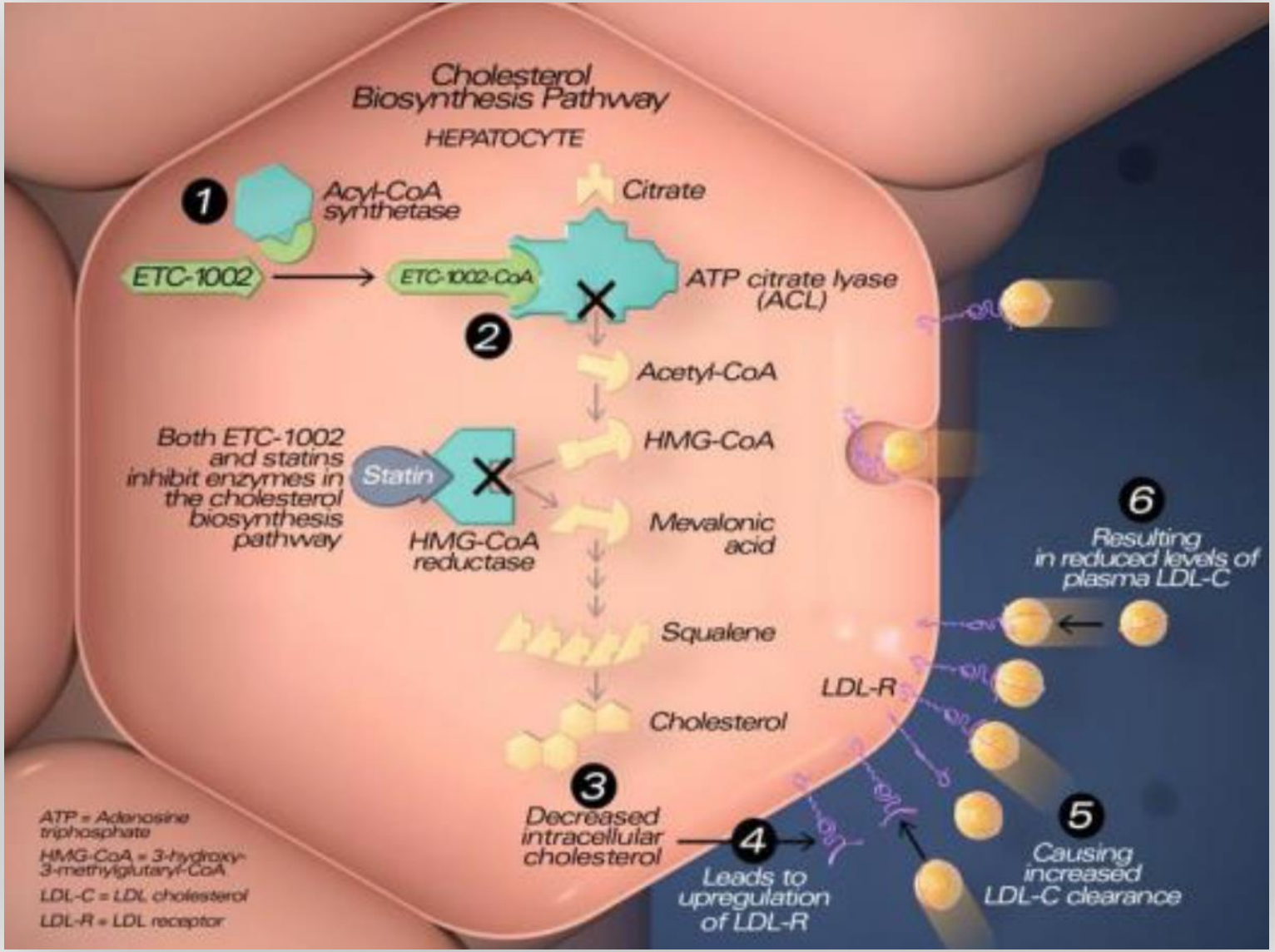
Statin discontinuation and CV morbidity and mortality



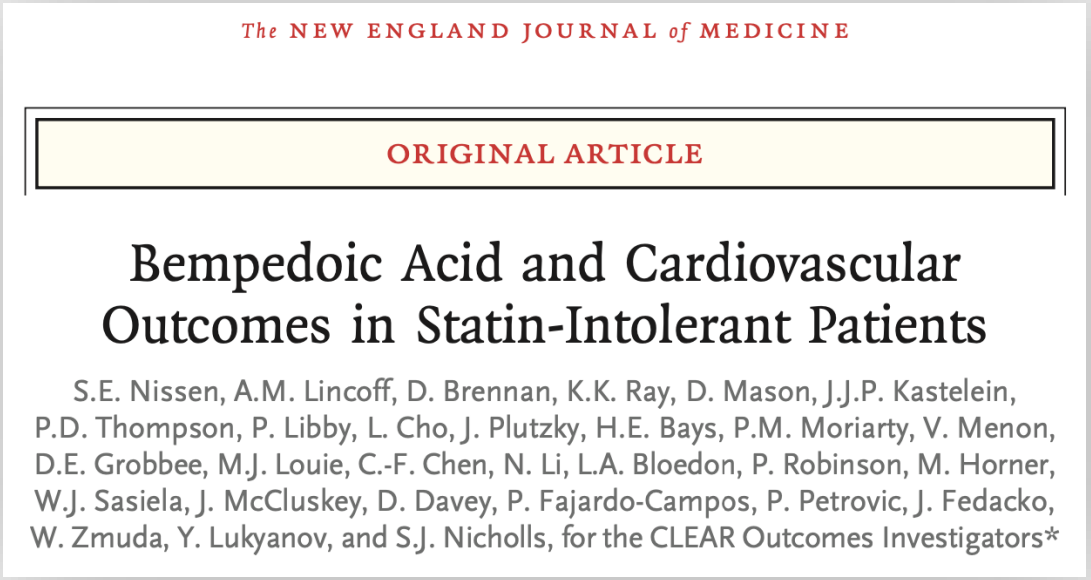
Arch Intern Med 2006;166:1842

Metabolism of Cholesterol Synthesis

Bempedoic acid



Bempedoic acid and CV outcomes in statin-intolerant patients: CLEAR Outcomes trial



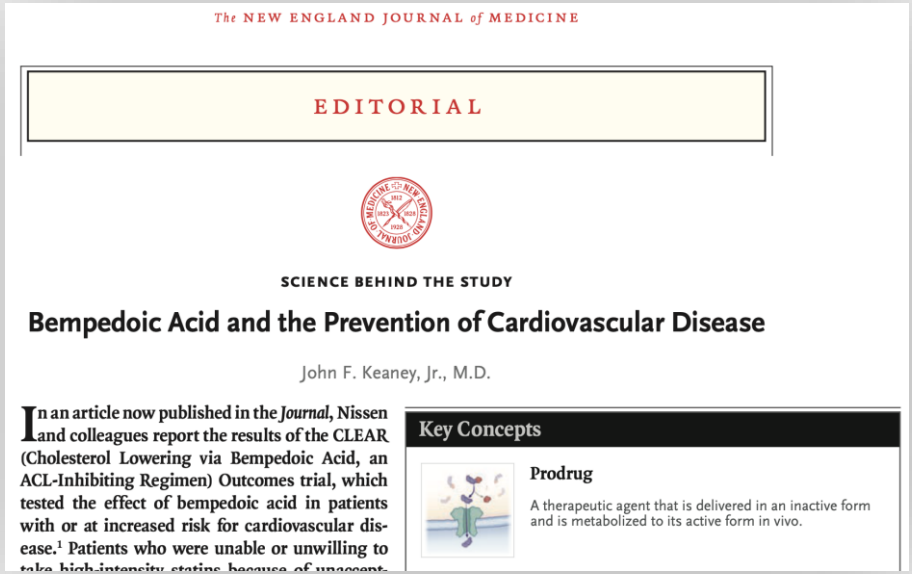
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

N Engl J Med 2023;388:1353-1364



The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

SCIENCE BEHIND THE STUDY

Bempedoic Acid and the Prevention of Cardiovascular Disease

John F. Keaney, Jr., M.D.

In an article now published in the *Journal*, Nissen and colleagues report the results of the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) Outcomes trial, which tested the effect of bempedoic acid in patients with or at increased risk for cardiovascular disease.[1] Patients who were unable or unwilling to

Key Concepts

Prodrug

A therapeutic agent that is delivered in an inactive form and is metabolized to its active form in vivo.

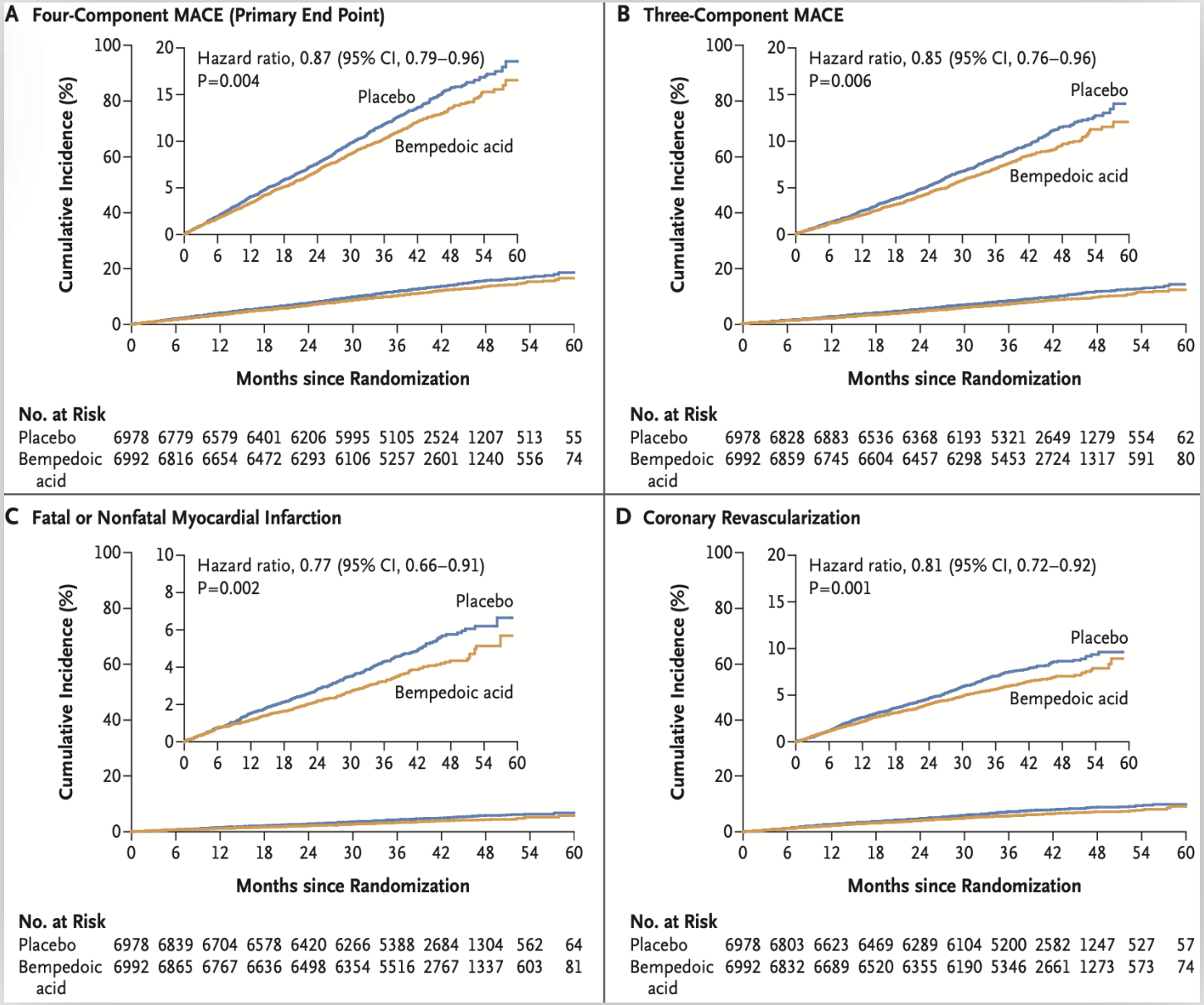
N Engl J Med 2023;388:1425-1426

Bempedoic acid to help statin !

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

N Engl J Med 2023;388:1353-1364



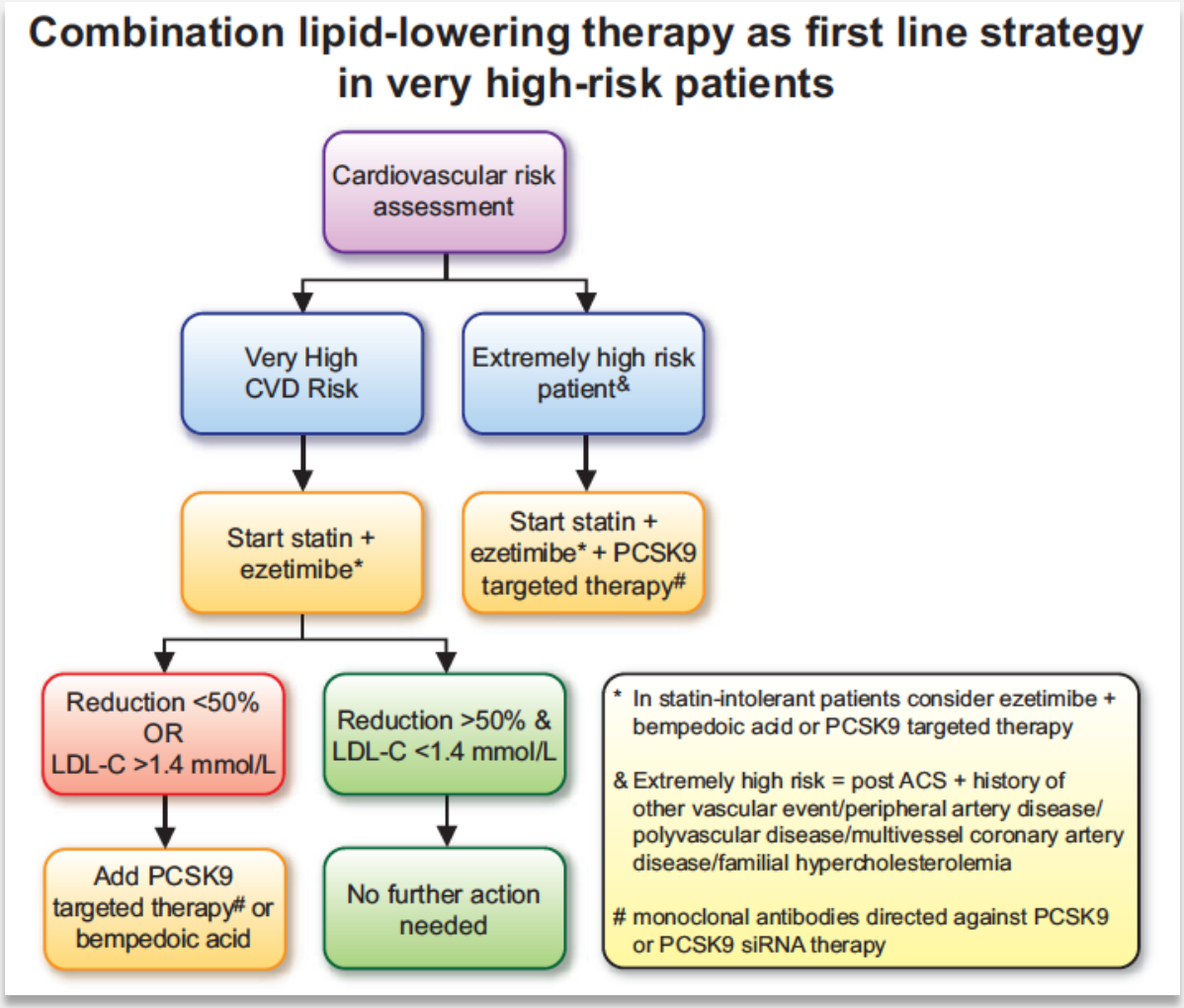
Combination therapy to better control blood lipid levels

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–4
doi:10.1093/eurheartj/ehab718

VIEWPOINT
Epidemiology and prevention

Combination lipid-lowering therapy as first-line strategy in very high-risk patients

Kausik K. Ray[1]*, Laurens F. Reeskamp [2], Ulrich Laufs [3], Maciej Banach [4], François Mach [5], Lale S. Tokgözoğlu [6], Derek L. Connolly[7], Anja J. Gerrits[8], Erik S. G. Stroes [2], Luis Masana [9], and John J. P. Kastelein [2]



Eur Heart J 2022;43:830

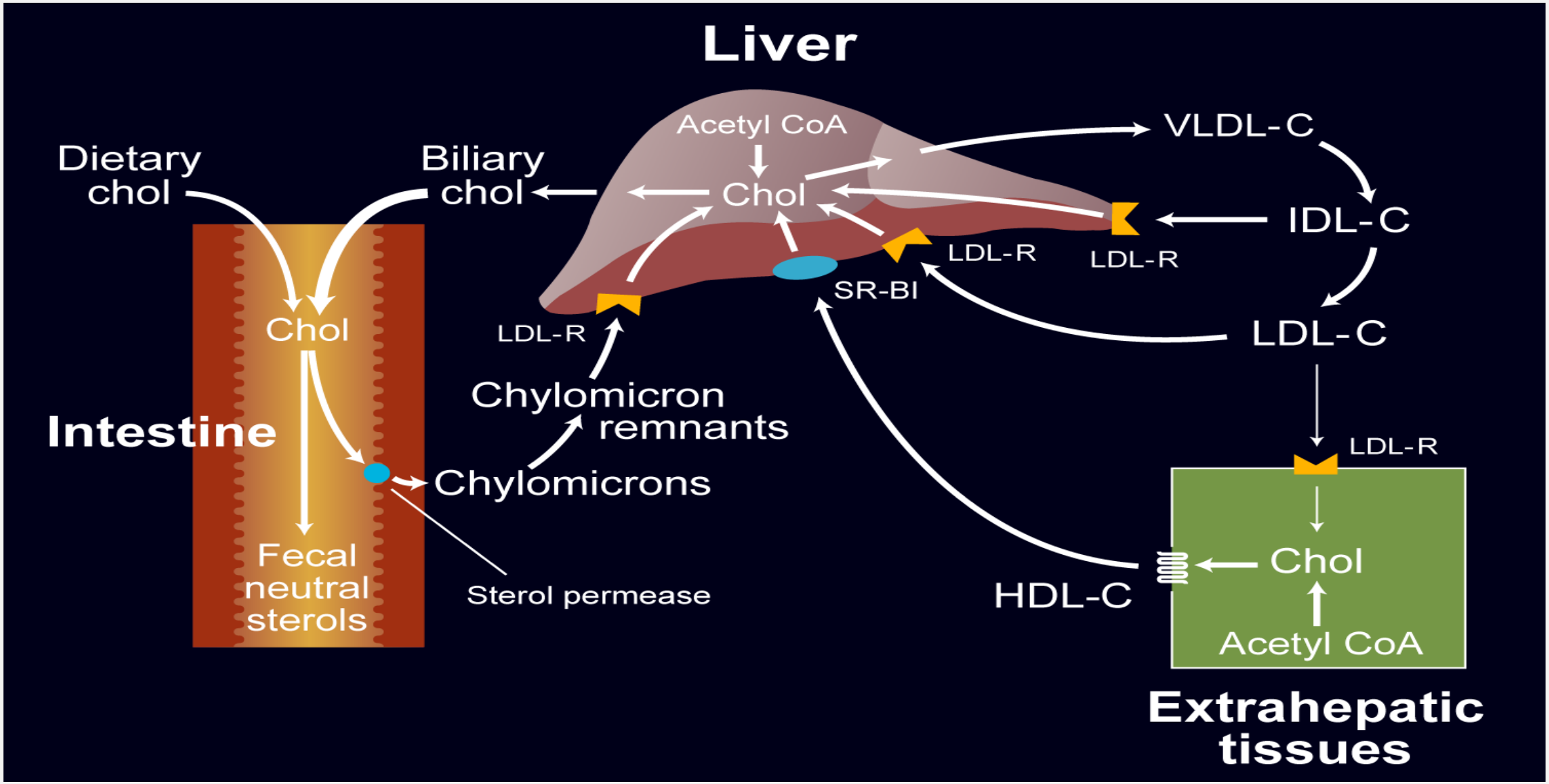
Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)

EAS ESC European Society of Cardiology

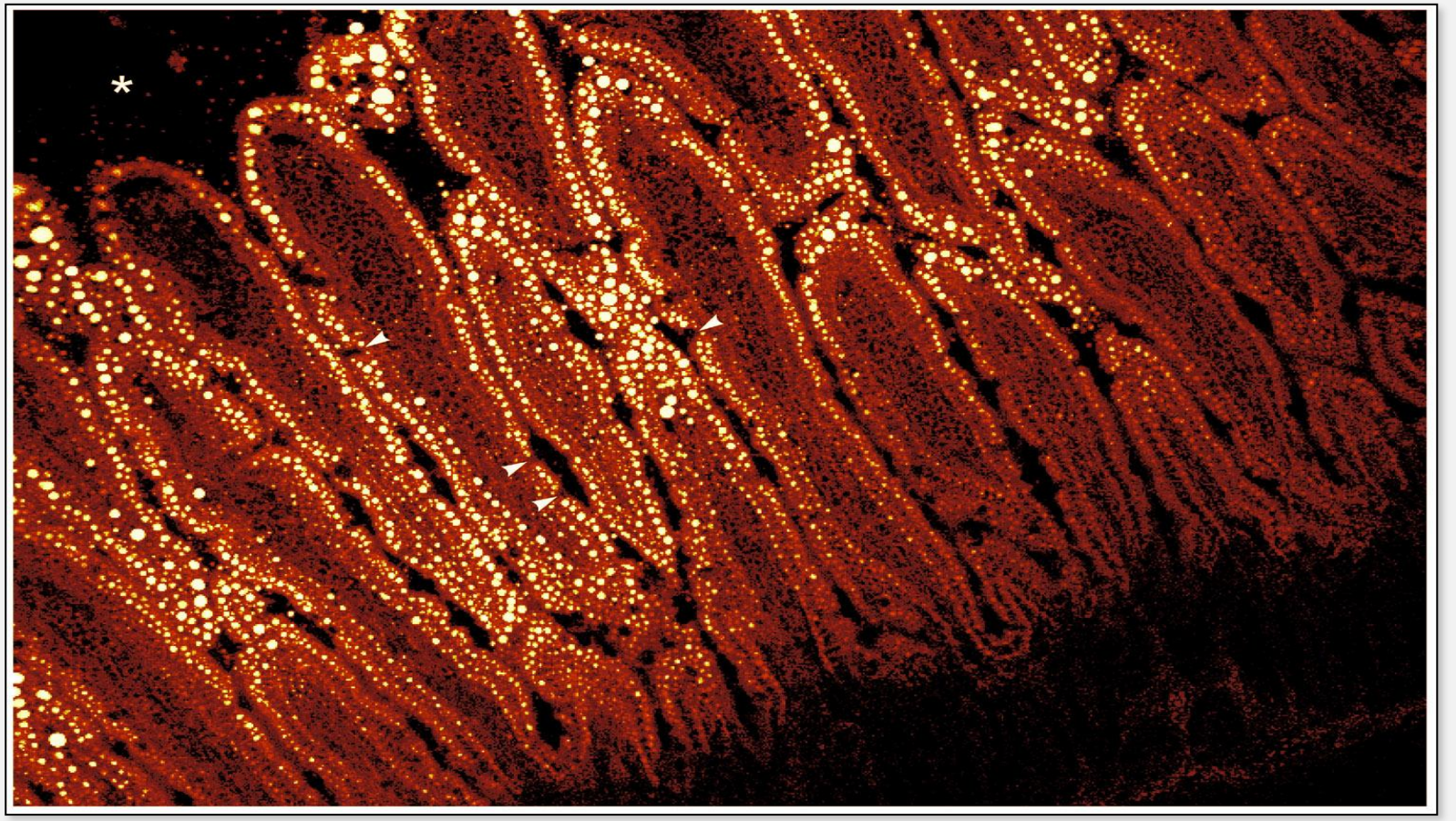
Recommendations	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals[c] set for the specific level of risk.	I	A
If the goals[c] are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	I	B

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Transport du Cholestérol



Absorption du Cholestérol



Absorption de cholestérol fluorescent par le petit intestin

*** lumière de l'intestin**

J Lipid Res 1999;10:1747

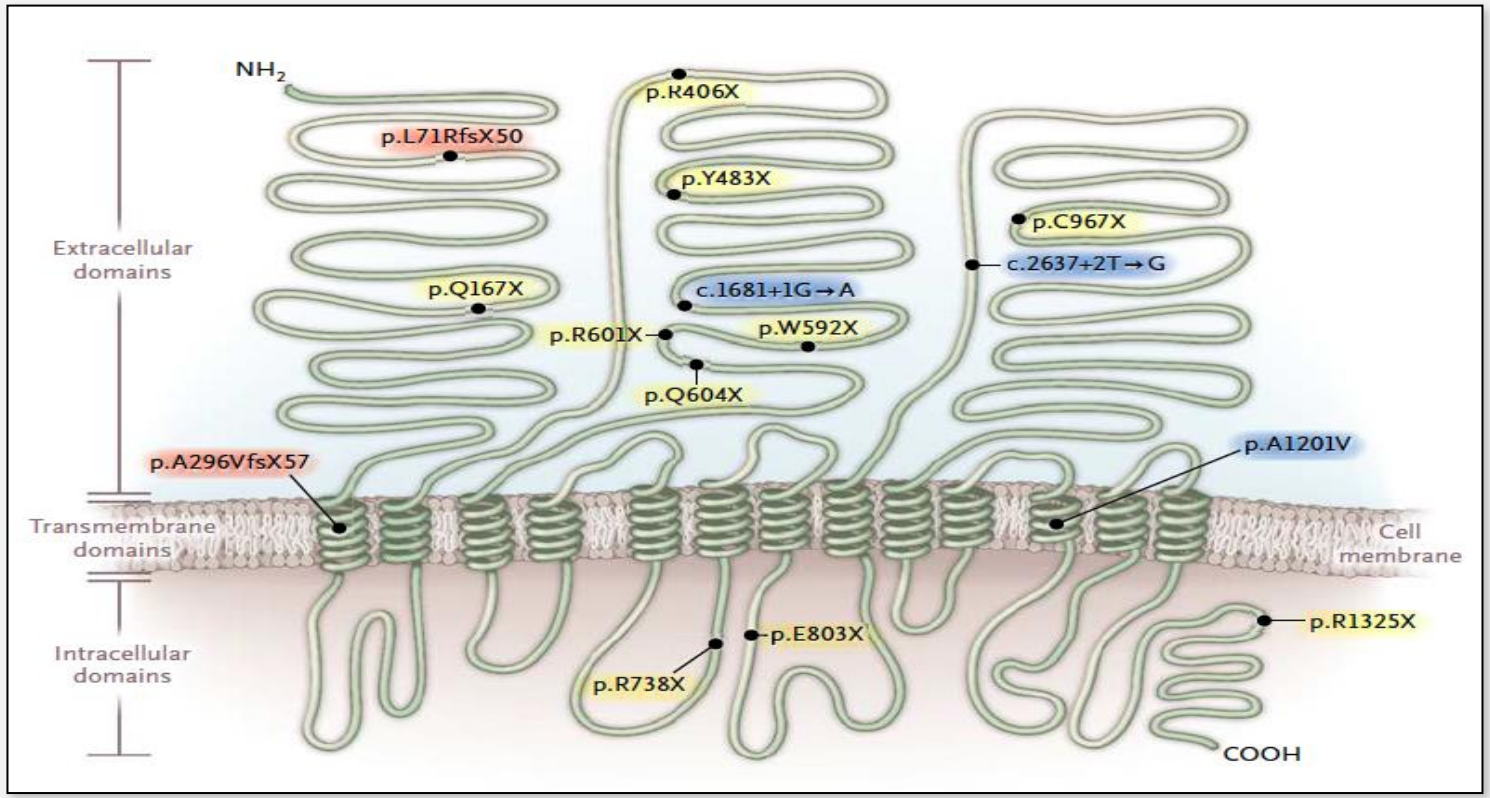
Pourquoi Ezetimibe ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inactivating Mutations in *NPC1L1* and Protection from Coronary Heart Disease

The Myocardial Infarction Genetics Consortium Investigators



New Engl J Med 2014;371:2072

Pourquoi Ezetimibe ?

Table 2. Association between the Presence of Inactivating Mutations in *NPC1L1* and Plasma Lipid Levels.*

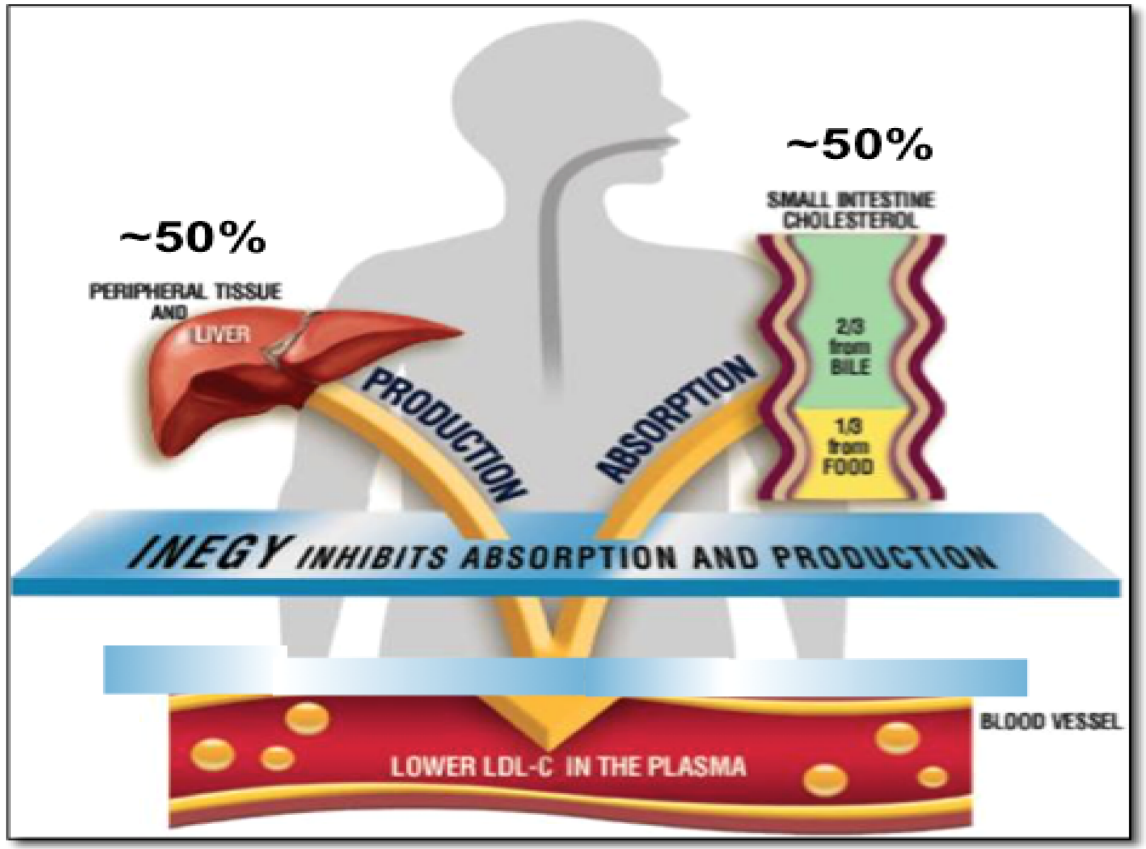
		Mean Difference between Carriers
Low-density lipoprotein	−12	0.04
High-density lipoprotein	2	0.29
Triglycerides (% change)	−12	0.11†

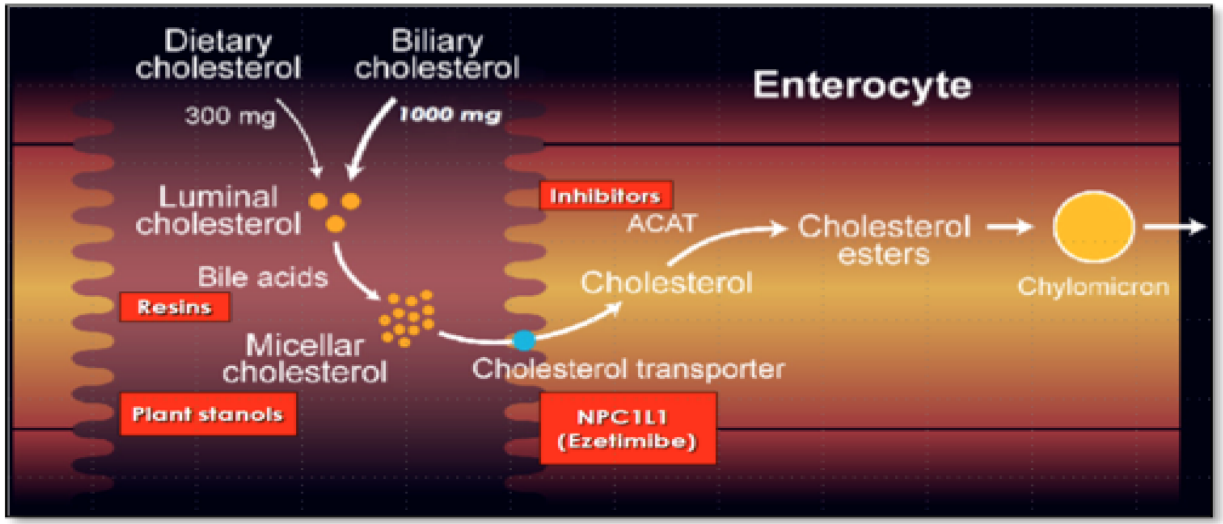
CONCLUSIONS

Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL cholesterol levels and a reduced risk of coronary heart disease. (Funded by the National Institutes of Health and others.)

New Engl J Med 2014;371:2072

Counter-regulation of cholesterol absorption and synthesis





	Statin[1]	Ezetimibe[1]	Statin + Ezetimibe
Cholesterol synthesis in liver	↓	↑	↓
Cholesterol absorption in intestine	↑	↓	↓

LDL-C: should we go lower after ACS ?

IMPROVE-IT Primary Endpoint - ITT

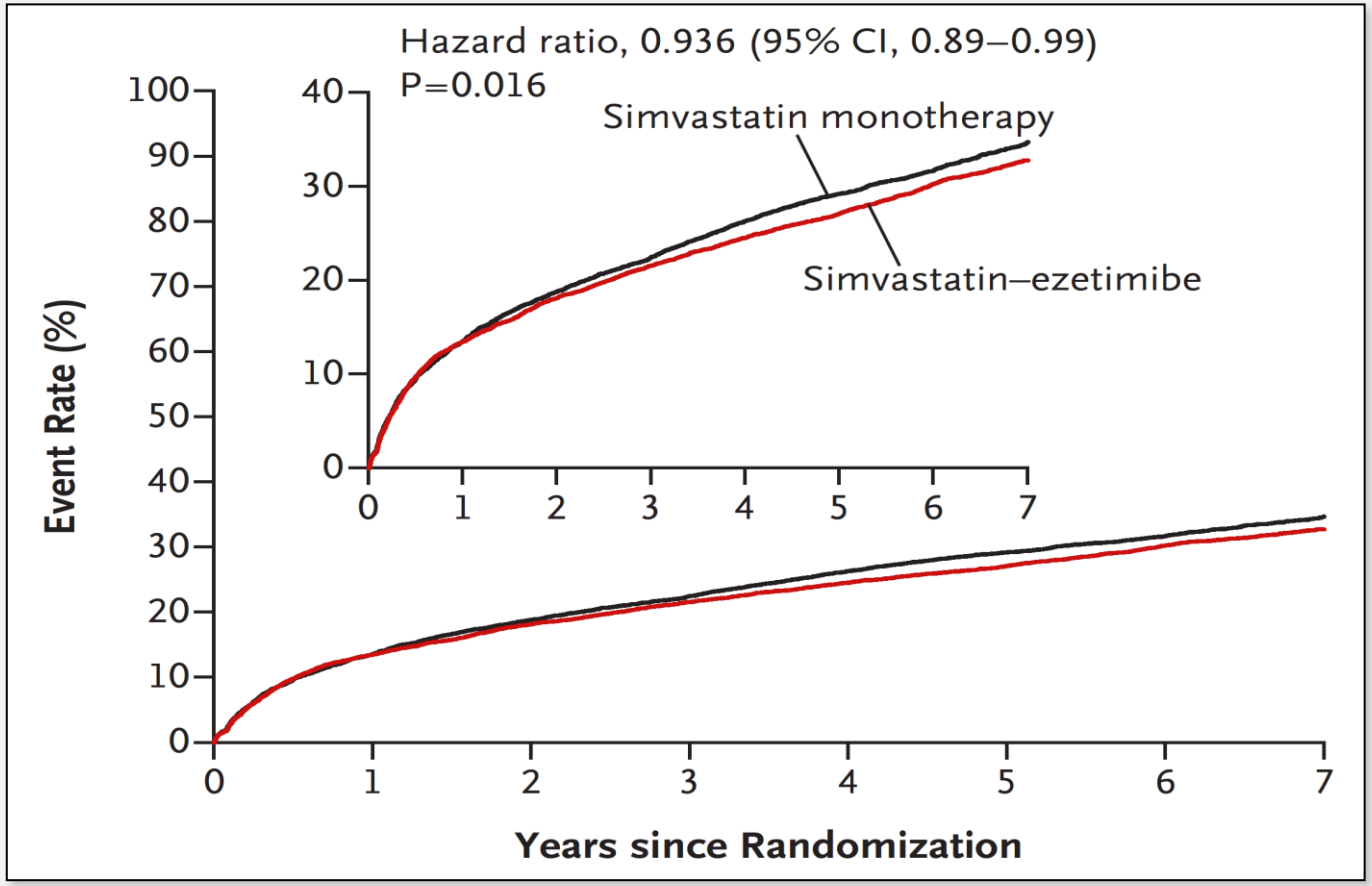
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*



N Engl J Med 2015;372:2387

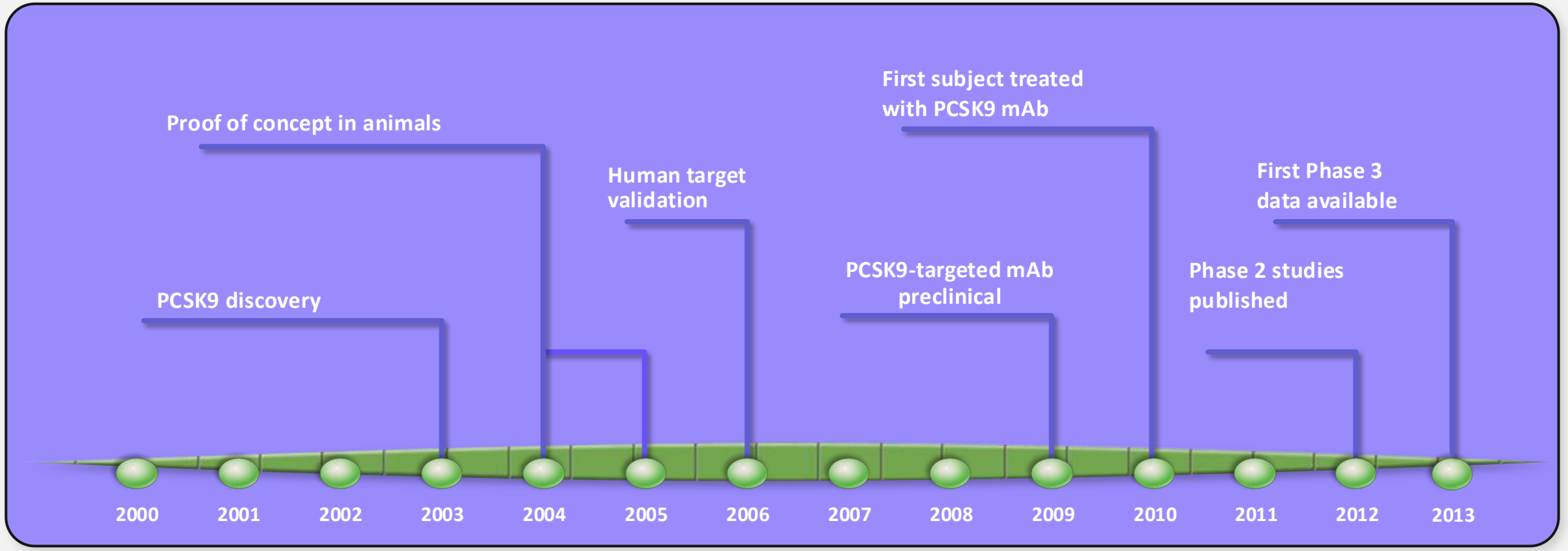
Recommendations for pharmacological low-density lipoprotein cholesterol lowering (2)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
For secondary prevention, patients at very-high risk not achieving their goal[c] on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

PCSK9 (Proprotein Convertase Subtilisin/Kexin 9)
Rapid progress from bench to clinic in less than a decade

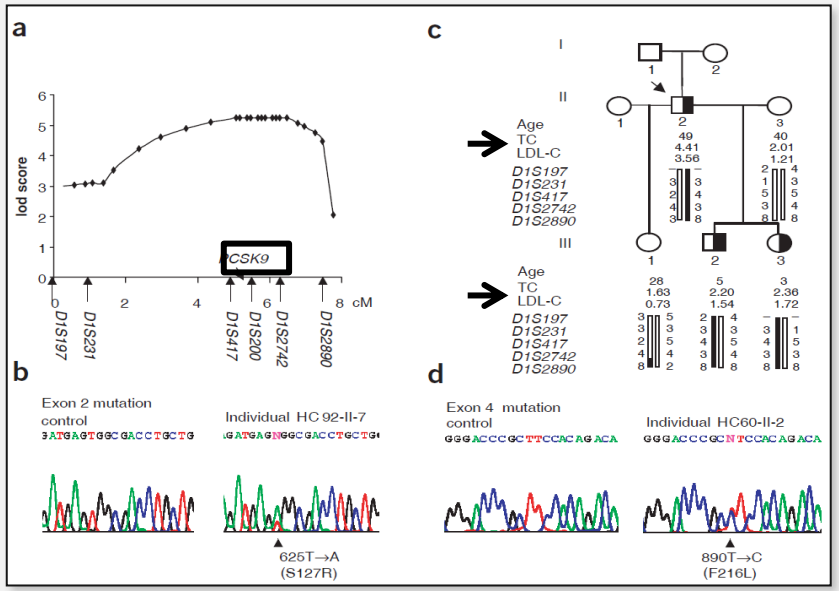


PCSK9 Gain Of Function mutations in humans

- 2 families with hypercholesterolemia
- The region between D1S197 and D1S2890 on chromosome 1 contains 41 genes, including PCSK9
- PCSK9 is related to PCSK1 which is known to be involved in cholesterol metabolism
- First demonstration in humans that PCSK9 is involved in cholesterol metabolism

Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia

Marianne Abifadel[1,2], Mathilde Varret[1], Jean-Pierre Rabès[1,3], Delphine Allard[1], Khadija Ouguerram[4], Martine Devillers[1], Corinne Cruaud[5], Suzanne Benjannet[6], Louise Wickham[6], Danièle Erlich[1], Aurélie Derré[1], Ludovic Villéger[1], Michel Farnier[7], Isabel Beucler[8], Eric Bruckert[9], Jean Chambaz[10], Bernard Chanu[11], Jean-Michel Lecerf[12], Gerald Luc[12], Philippe Moulin[13], Jean Weissenbach[5], Annick Prat[6], Michel Krempf[4], Claudine Junien[1,3], Nabil G Seidah[6] & Catherine Boileau[1,3]



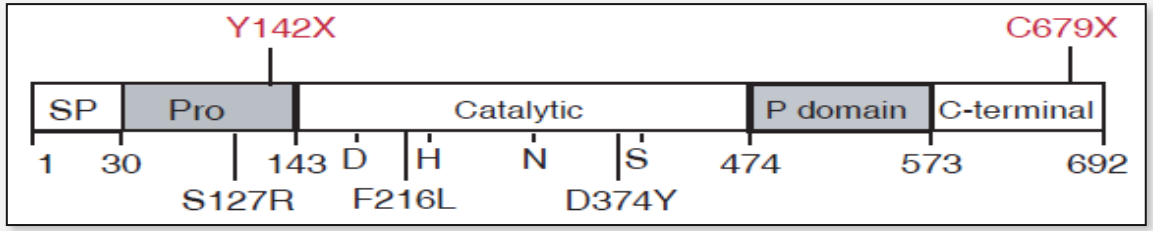
Nature Genetics 2003;34:154

PCSK9 Loss Of Function mutations in humans

Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in *PCSK9*

Jonathan Cohen[1–3], Alexander Pertsemlidis[2,3], Ingrid K Kotowski[4], Randall Graham[1], Christine Kim Garcia[1–3] & Helen H Hobbs[1–4]

- Coding region in 128 subjects with low LDL-C levels sequenced
- 5 missense mutations in PCSK9 gene identified (Y142X and C679X)
- Mutations in approximately 2% Africa Americans and 0.1% Caucasians



Nature Genetics 2005;37:161

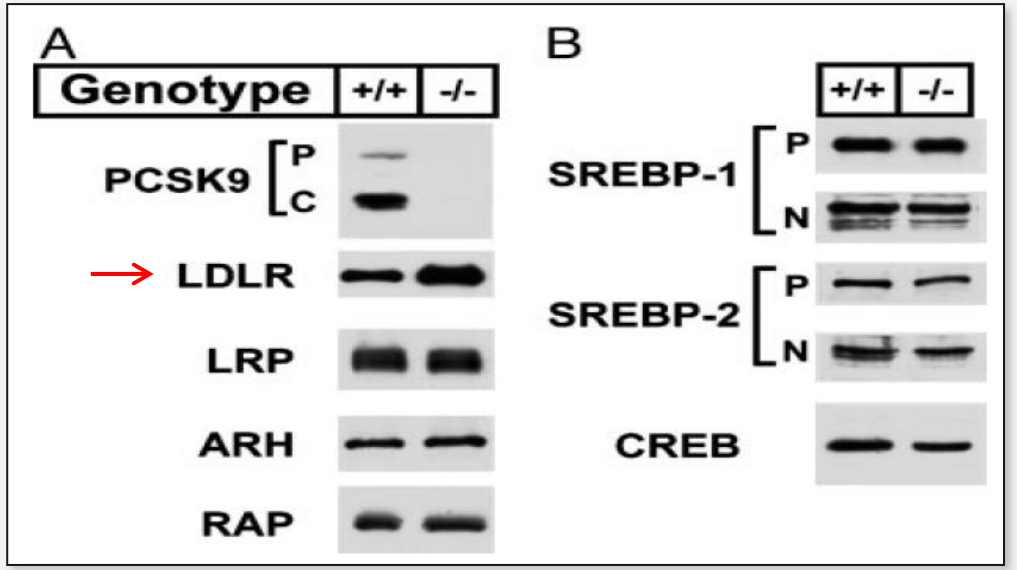
Cholesterol metabolism in PCSK9 knock-out mice

- Serum cholesterol is less than 50% in PCSK9$^{-/-}$ mice
- This is due to a decreased in LDL-C which is associated with increased expression of the LDLR

Decreased plasma cholesterol and hypersensitivity to statins in mice lacking *Pcsk9*

Shirya Rashid*, David E. Curtis*, Rita Garuti*, Norma N. Anderson*, Yuriy Bashmakov*, Y. K. Ho*, Robert E. Hammer†, Young-Ah Moon*, and Jay D. Horton*‡§

Parameter	WT	*Pcsk9*$^{-/-}$
No. of mice	4	4
Body weight, g	25.5 ± 0.6	30.0 ± 1.6
Liver cholesterol, mg/g	2.20 ± 0.16	2.00 ± 0.02
Liver TG, mg/g	9.2 ± 0.6	7.2 ± 0.7
Plasma cholesterol, mg/dl	95.7 ± 9.4	→ 46.3 ± 1.9*
Plasma TG, mg/dl	70.0 ± 11	85.8 ± 7.5



PNAS 2005;102:5374

PCSK9 loss of function mutation and very low LDL-C from birth

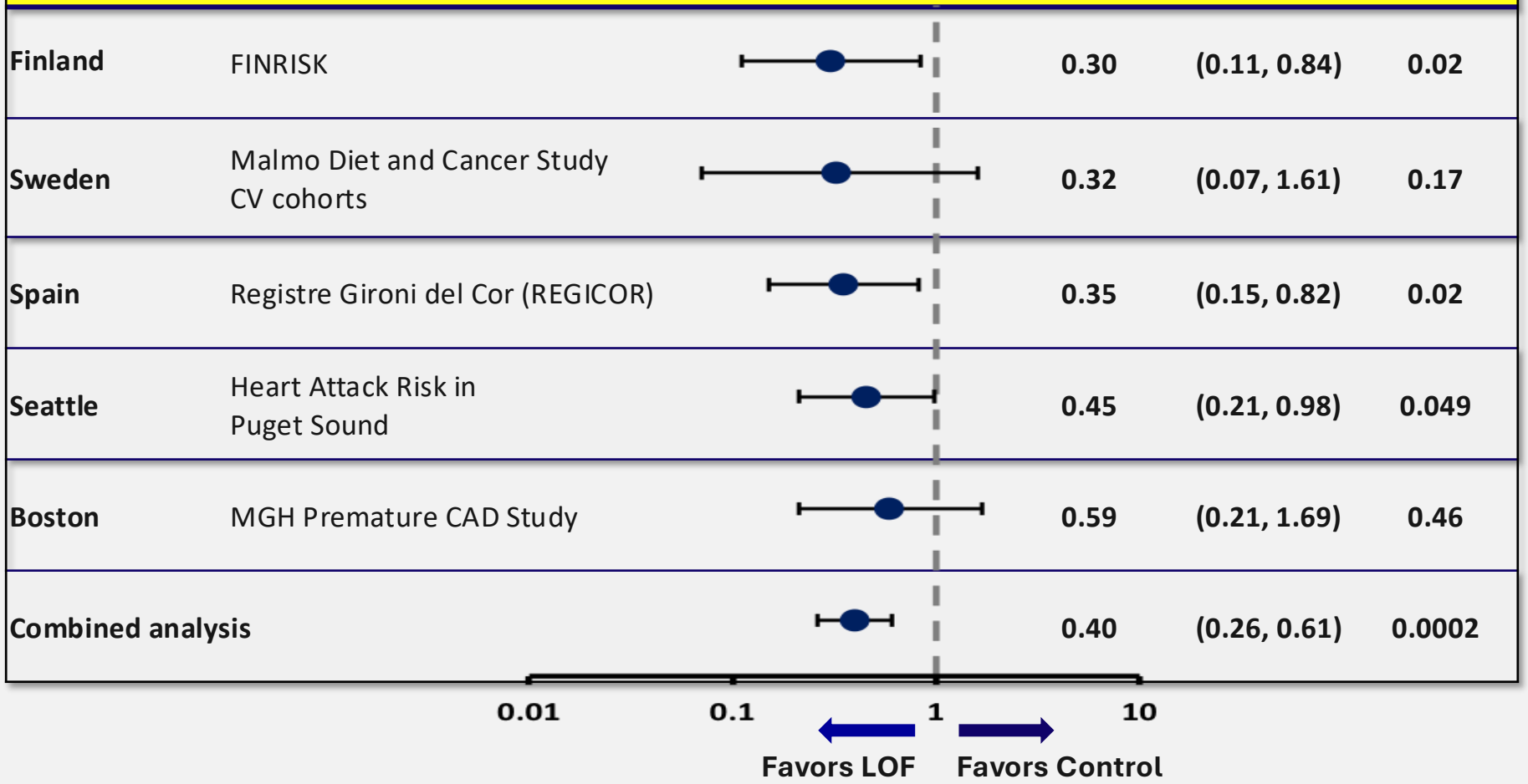
Am J Hum Genetics 2006;79:514
32 yo woman
Compound heterozygote for 2 LOF alleles in PCSK9
LDL-C 0.36 mmol/L (13.92 mg/dL)
Fertile, college educated, physically coordinated (fitness instructor)

Atherosclerosis 2007;193:445
African woman
Homozygote C679X
LDL-C 0.40 mmol/L (15.47 mg/dL)
Healthy with children

Impact of PCSK9 Loss of Function mutation on risk of MI

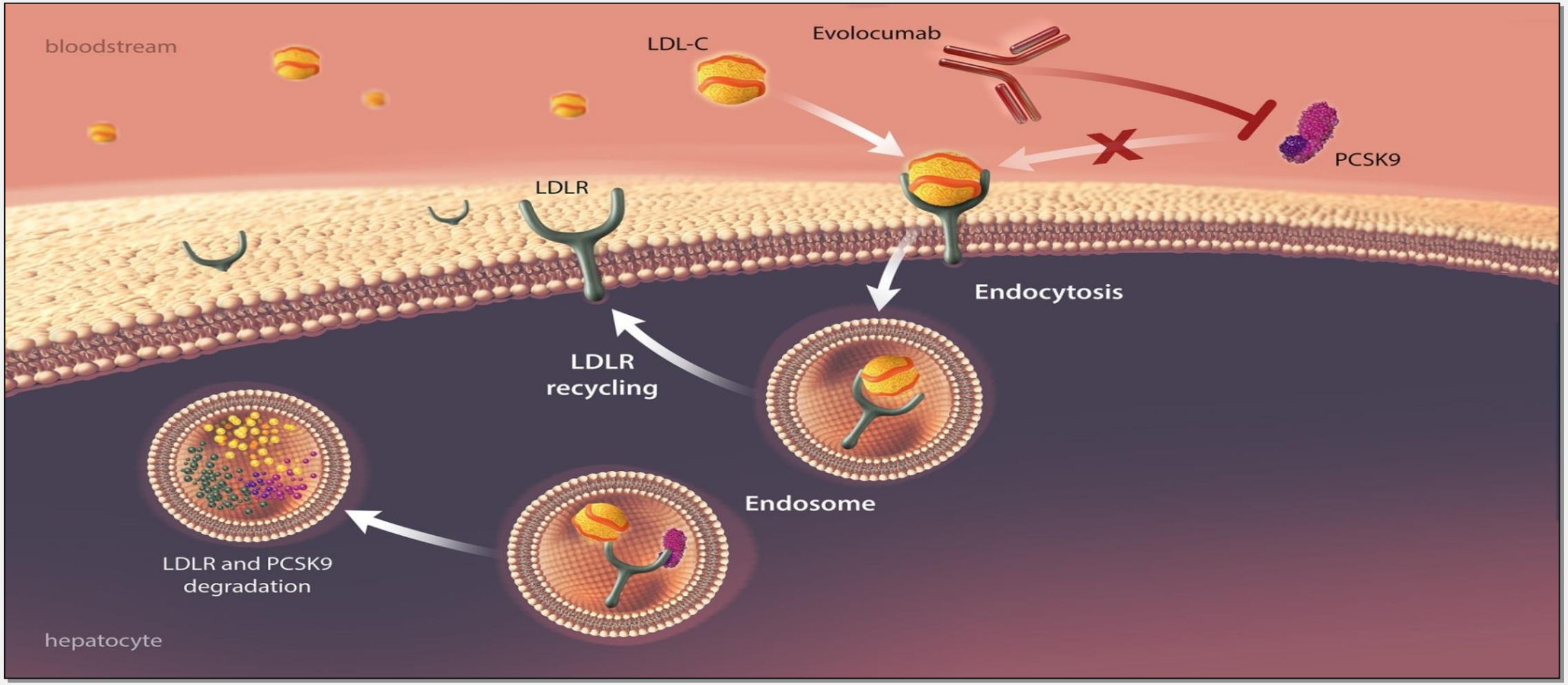
Lifelong impact of 16% lower LDL translates into 60% lower risk

Site	Study	OR for MI	95% CI	p-value
Finland	FINRISK	0.30	(0.11, 0.84)	0.02
Sweden	Malmo Diet and Cancer Study CV cohorts	0.32	(0.07, 1.61)	0.17
Spain	Registre Gironi del Cor (REGICOR)	0.35	(0.15, 0.82)	0.02
Seattle	Heart Attack Risk in Puget Sound	0.45	(0.21, 0.98)	0.049
Boston	MGH Premature CAD Study	0.59	(0.21, 1.69)	0.46
Combined analysis		0.40	(0.26, 0.61)	0.0002



N Engl J Med 2008;358:2299

Fully human monoclonal antibody against PCSK9 inhibits PCSK9/LDL-R interaction



PNAS USA 2009;106:9820

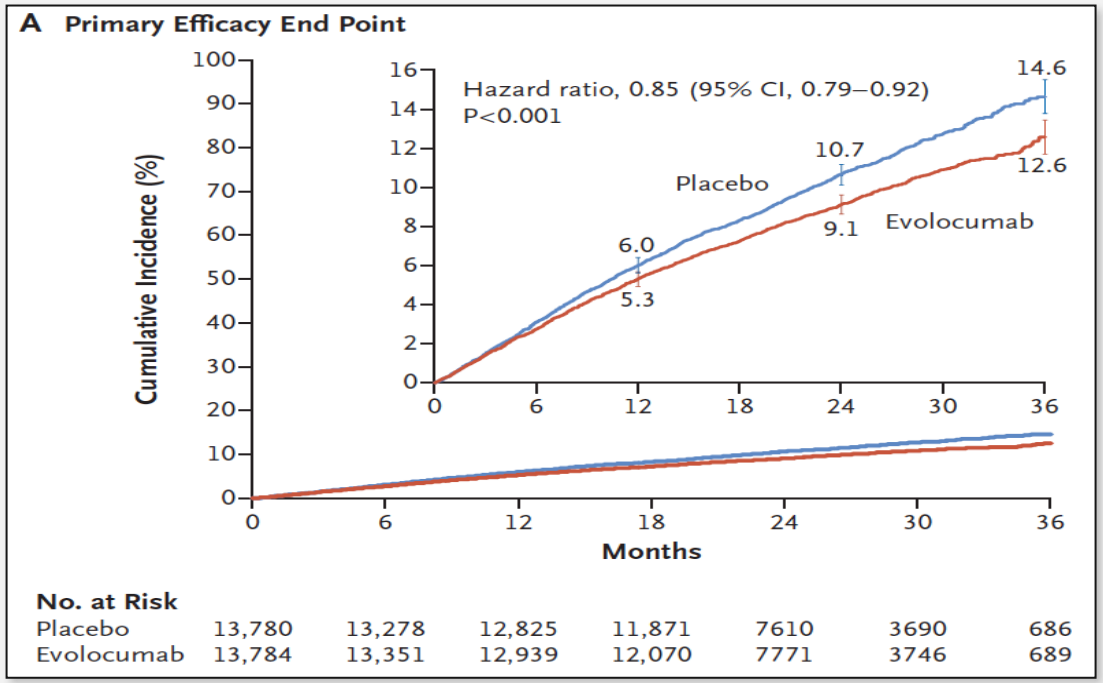
PCSK9 mAb and CV events

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

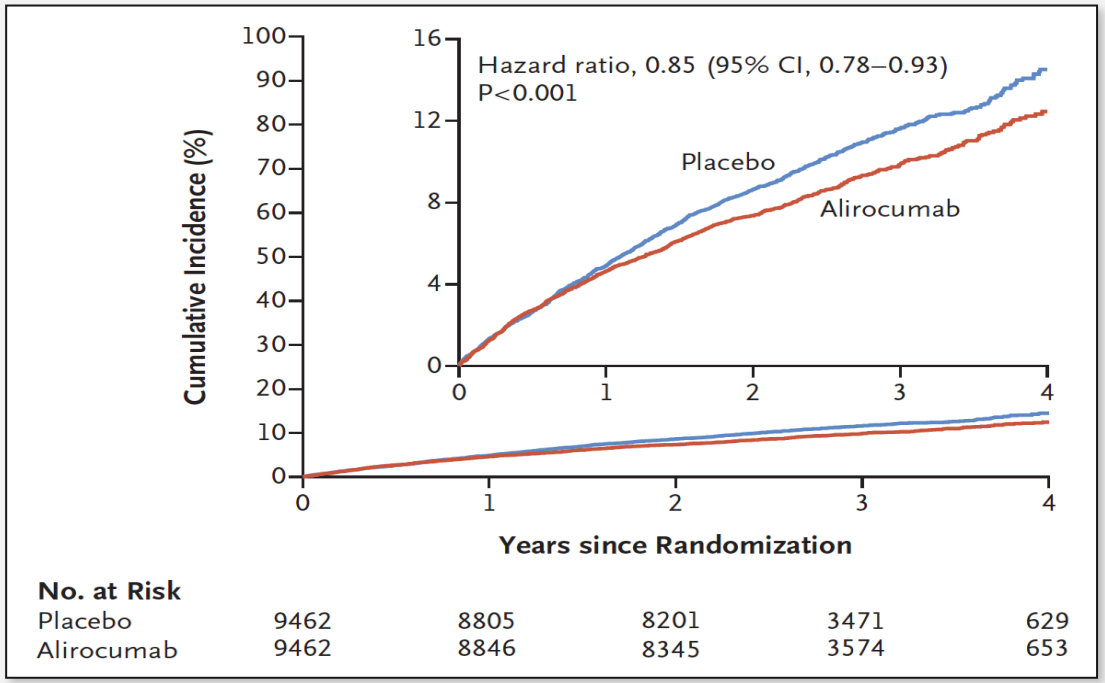


New Engl J Med 2017;376:1713

ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*



N Engl J Med 2018;379:2097

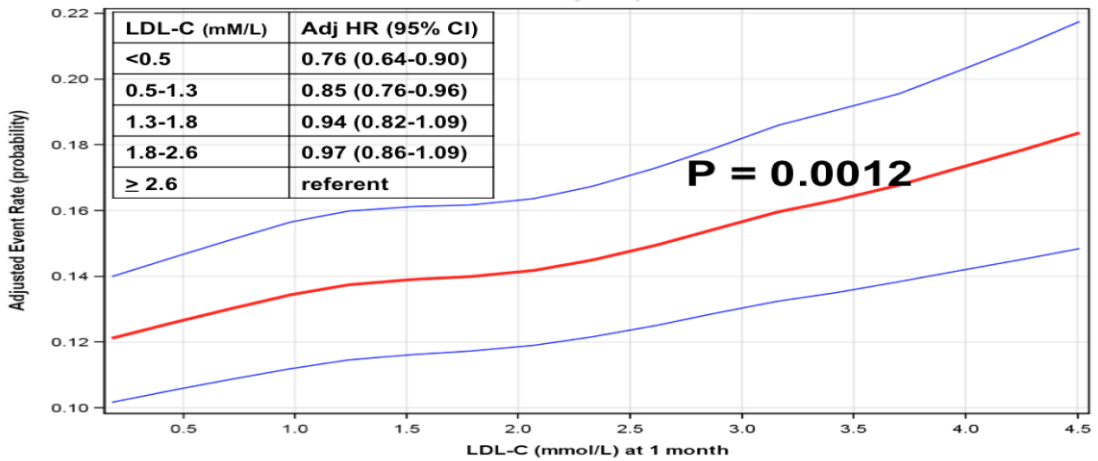
PCSK9 mAb (evolocumab) and CV events

Clinical efficacy and safety of achieving very low LDL-CLDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab (FOURIER trial)

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Ioanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian Ott, Estella Kanevsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine; on behalf of the FOURIER Investigators

Primary Efficacy Endpoint*

LDL-C (mM/L)	Adj HR (95% CI)
<0.5	0.76 (0.64-0.90)
0.5-1.3	0.85 (0.76-0.96)
1.3-1.8	0.94 (0.82-1.09)
1.8-2.6	0.97 (0.86-1.09)
≥ 2.6	referent



*CV death, MI, stroke, hospitalization for UA, coronary revasc

Exploratory Analysis – 1 Achieved LDL-C <0.4 mM/L*

	LDL-C at 4 Weeks			
	<0.4 (N=1335)	≥2.6 (N=4395)		
	n (%)	n (%)	Adjusted HR (95% CI)	P
Efficacy Endpoints				
CVD, MI, stroke, UA, cor revasc	105 (7·9)	521 (11·9)	0·71 (0·56-0·89)	0·003
CV death, MI, stroke	66 (4·9)	345 (7·8)	0·66 (0·50-0·88)	0·005
Safety Endpoints				
Serious AE	313 (23·4)	1022 (23·3)	0·96 (0·81-1·13)	0·63
AE -> drug DC	42 (3·1)	149 (3·4)	0·89 (0·60-1·32)	0·56

Lancet 2017;390:1962

Coronary imaging study

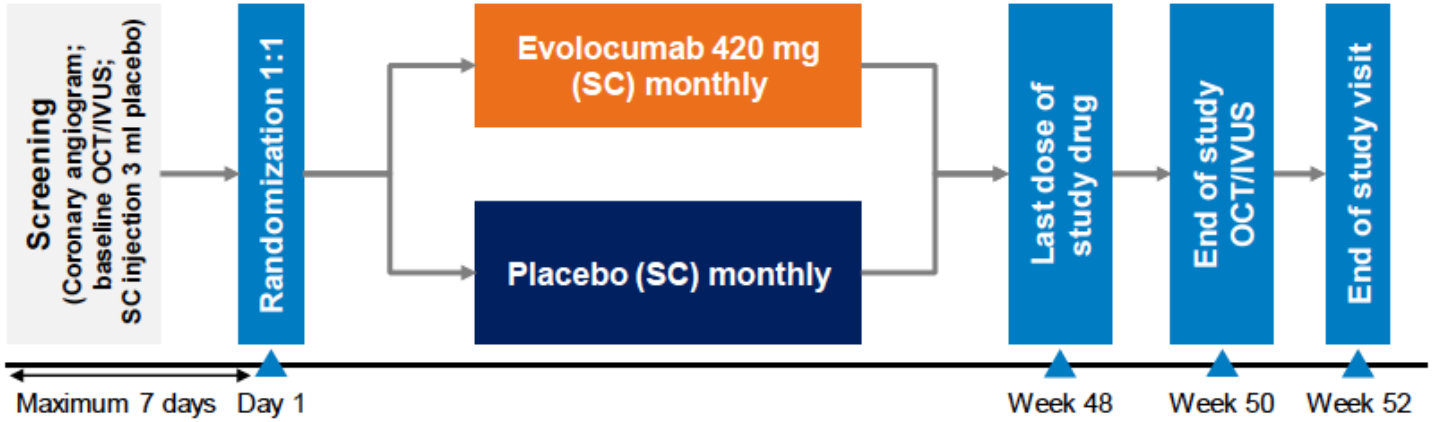
Effect of Evolocumab on Changes in Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction: The HUYGENS Randomized Clinical Trial

Aim: To evaluate the impact of PCSK9 inhibition with evolocumab on coronary atheroma phenotype post-ACS[1,2]

Inclusion Criteria[1,2]

- NSTEMI
- Angiographic CAD
- LDL-C ≥ 1.6 mmol/L on high-intensity statin, ≥ 2.1 mmol/L on low-/moderate-intensity statin, or ≥ 3.4 mmol/L on no statin at screening
- Subsequently treated with maximally tolerated statin
- At least one OCT image with an FCT ≤ 120 µm and one image with lipid arc > 90° in a segment ≥ 40 mm in length[a]

Study Design[2]



Primary Endpoint[1]

Nominal change in minimum FCT in a matched arterial segment from baseline to week 50

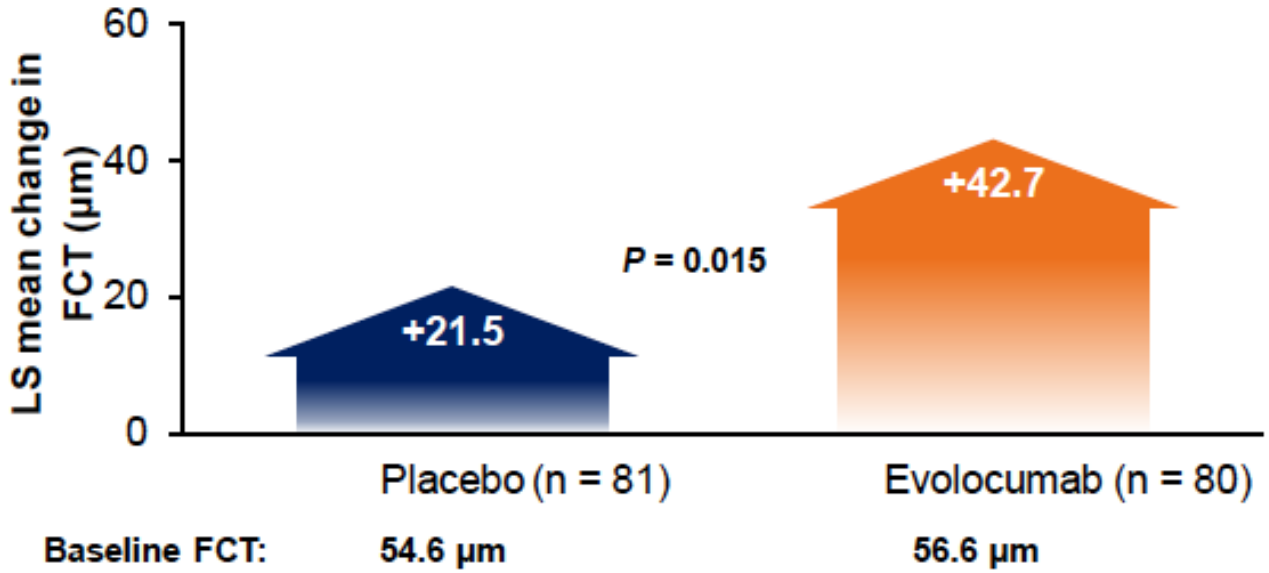
Secondary Endpoints[1]

- Percent change in minimum FCT
- Absolute change in the average of the minimum FCT for all images
- Absolute change in the maximum lipid arc

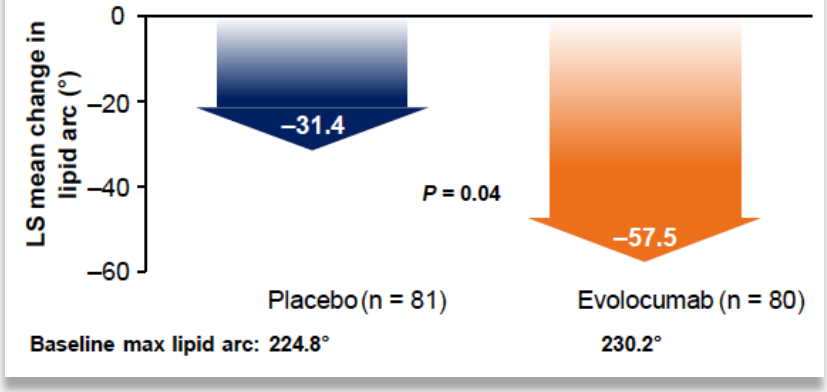
JACC Imag. 2022;15:1308

huygens

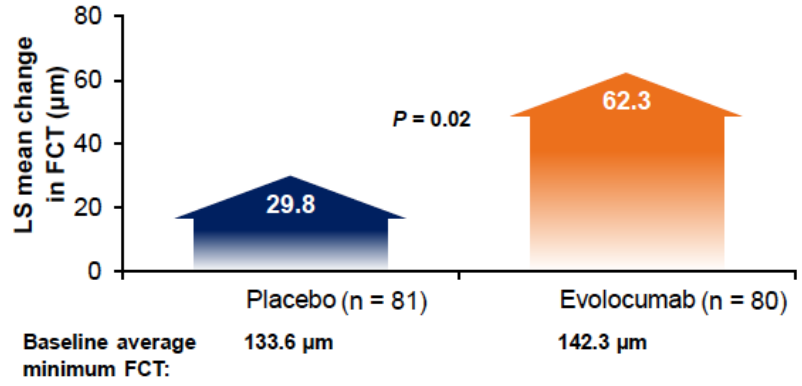
HUYGENS Primary Endpoint: Minimum FCT[1]



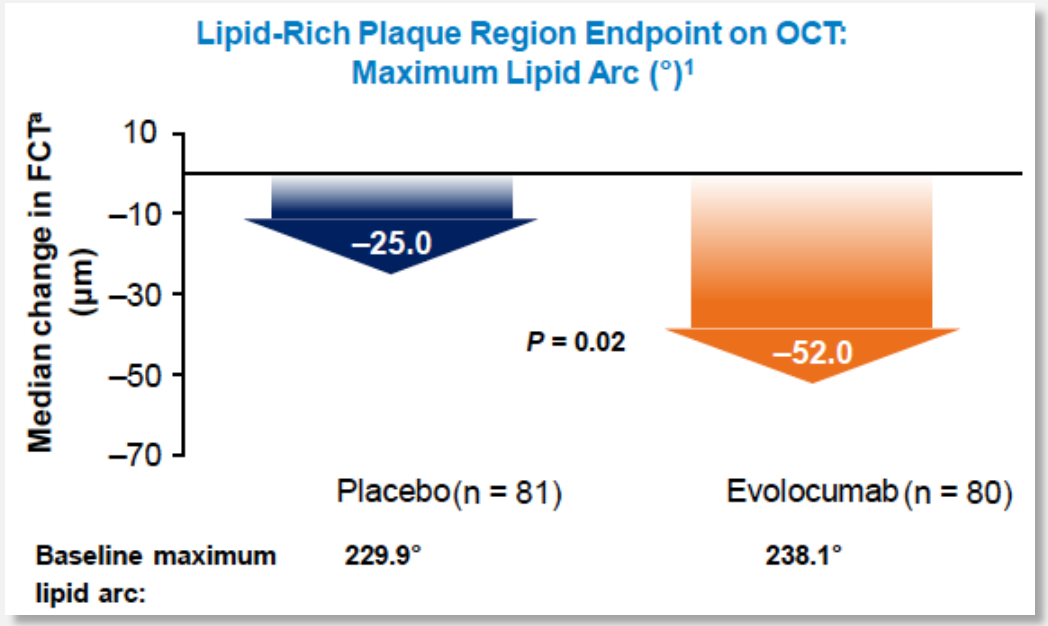
HUYGENS Secondary Endpoint: Maximum Lipid Arc[1]

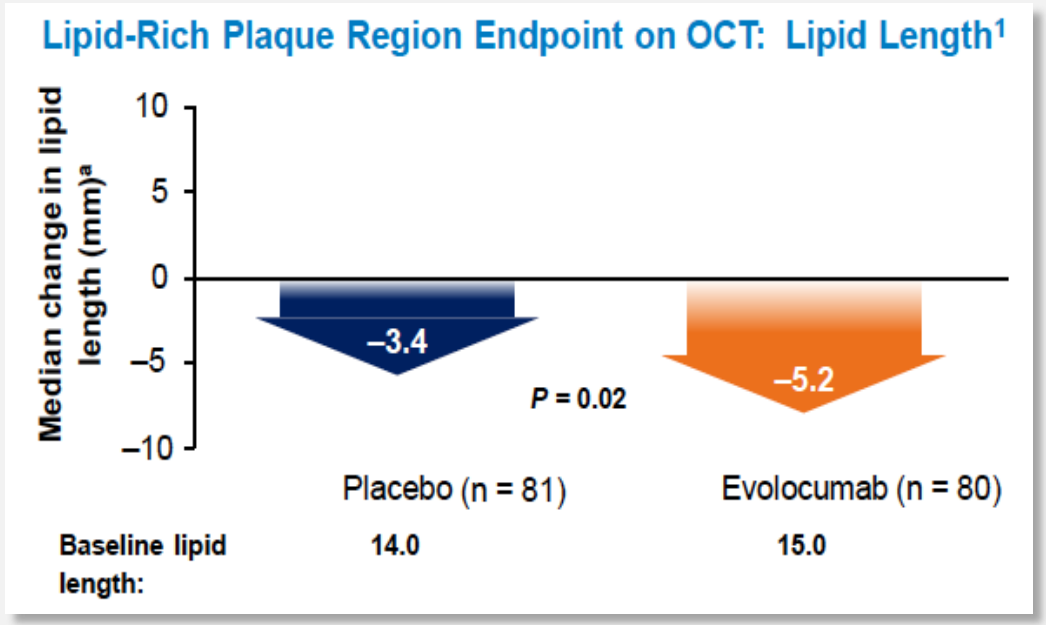


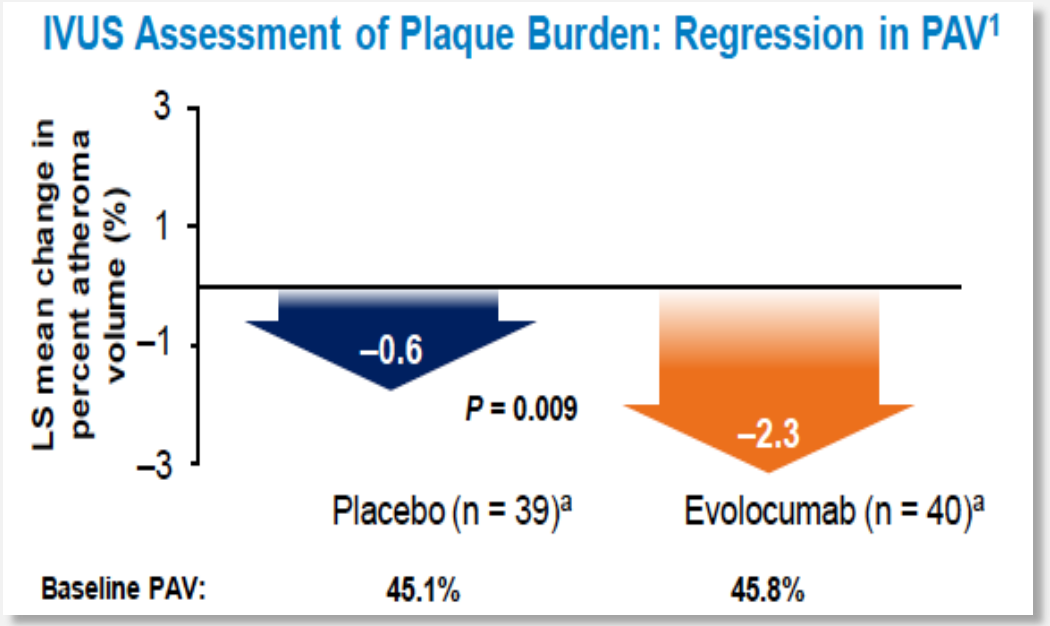
HUYGENS Secondary Endpoint: Average Minimum FCT for All Images[1]



JACC Imag. 2022;15:1308







JACC Imag. 2022;15:1308

ORIGINAL RESEARCH

Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the effect of evolocumab on optical coherence tomography (OCT) measures of plaque composition.

BACKGROUND The proprotein convertase subtilisin kexin type-9 inhibitor evolocumab produced coronary atheroma regression in statin-treated patients.

METHODS Patients with a non-ST-segment elevation myocardial infarction were treated with monthly evolocumab 420 mg (n = 80) or placebo (n = 81) for 52 weeks. Patients underwent serial OCT and intravascular ultrasound imaging within a matched arterial segment of a nonculprit vessel. The primary analysis determined the change in the minimum fibrous cap thickness and maximum lipid arc throughout the imaged arterial segment. Additional analyses determined changes in OCT features in lipid-rich plaque regions and plaque burden. Safety and tolerability were evaluated.

RESULTS Among treated patients, (age 60.5 ± 9.6 years; 28.6% women; low-density lipoprotein cholesterol [LDL-C], 141.3 ± 33.1 mg/dL), 135 had evaluable imaging at follow-up. The evolocumab group achieved lower LDL-C levels (28.1 vs 87.2 mg/dL; $P < 0.001$). The evolocumab group demonstrated a greater increase in minimum fibrous cap thickness (+42.7 vs +21.5 μm; $P = 0.015$) and decrease in maximum lipid arc (−57.5° vs. −31.4°; $P = 0.04$) and macrophage index (−3.17 vs −1.45 mm; $P = 0.04$) throughout the arterial segment. Similar benefits of evolocumab were observed in lipid-rich plaque regions. Greater regression of percent atheroma volume was observed with evolocumab compared with placebo (−2.29% ± 0.47% vs −0.61% ± 0.46%; $P = 0.009$). The groups did not differ regarding changes in microchannels or calcium.

CONCLUSIONS The combination of statin and evolocumab after a non-ST-segment elevation myocardial infarction produces favorable changes in coronary atherosclerosis consistent with stabilization and regression. This demonstrates a potential mechanism for the improved clinical outcomes observed achieving very low LDL-C levels following an acute coronary syndrome. (Imaging of Coronary Plaques in Participants Treated With Evolocumab; NCT03570697)
(J Am Coll Cardiol Img 2022;■:■–■)

huygens

Conclusions

- HUYGENS demonstrated that the combination of evolocumab and statin therapy after an NSTEMI produces favorable changes in coronary atherosclerosis, consistent with stabilization and regression
- Role of intensive lipid lowering is supported by observations of a direct relationship between the degree of LDL-C lowering or achieved LDL-C levels and increasing FCT
- Early administration of a PCSK9 inhibitor was well tolerated and demonstrated a potential mechanism for the improved clinical outcomes in patients who achieve very low LDL-C levels following an ACS

JACC Imag. 2022;15:1308

JAMA | Original Investigation

Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction
The PACMAN-AMI Randomized Clinical Trial

Lorenz Räber, MD, PhD; Yasushi Ueki, MD, PhD; Tatsuhiko Otsuka, MD; Sylvain Losdat, PhD; Jonas D. Häner, MD; Jacob Lonborg, MD; Gregor Fahrni, MD; Juan F. Iglesias, MD; Robert-Jan van Geuns, MD, PhD; Anna S. Ondracek, MSc; Maria D. Radu Juul Jensen, MD, PhD; Christian Zanchin, MD, PhD; Stefan Stortecky, MD; David Spirk, MD; George C. M. Siontis, MD, PhD; Lanja Saleh, PhD; Christian M. Matter, MD; Joost Daemen, MD, PhD; François Mach, MD; Dik Heg, PhD; Stephan Windecker, MD; Thomas Engstrøm, MD, PhD; Irene M. Lang, MD; Konstantinos C. Koskinas, MD, MSc; for the PACMAN-AMI collaborators

OBJECTIVE To determine the effects of alirocumab on coronary atherosclerosis using serial multimodality intracoronary imaging in patients with acute myocardial infarction.

DESIGN, SETTING, AND PARTICIPANTS The PACMAN-AMI double-blind, placebo-controlled, randomized clinical trial (enrollment: May 9, 2017, through October 7, 2020; final follow-up: October 13, 2021) enrolled 300 patients undergoing percutaneous coronary intervention for acute myocardial infarction at 9 academic European hospitals.

INTERVENTIONS Patients were randomized to receive biweekly subcutaneous alirocumab (150 mg; n = 148) or placebo (n = 152), initiated less than 24 hours after urgent percutaneous coronary intervention of the culprit lesion, for 52 weeks in addition to high-intensity statin therapy (rosuvastatin, 20 mg).

MAIN OUTCOMES AND MEASURES Intravascular ultrasonography (IVUS), near-infrared spectroscopy, and optical coherence tomography were serially performed in the 2 non–infarct-related coronary arteries at baseline and after 52 weeks. The primary efficacy end point was the change in IVUS-derived percent atheroma volume from baseline to week 52. Two powered secondary end points were changes in near-infrared spectroscopy–derived maximum lipid core burden index within 4 mm (higher values indicating greater lipid content) and optical coherence tomography–derived minimal fibrous cap thickness (smaller values indicating thin-capped, vulnerable plaques) from baseline to week 52.

RESULTS Among 300 randomized patients (mean [SD] age, 58.5 [9.7] years; 56 [18.7%] women; mean [SD] low-density lipoprotein cholesterol level, 152.4 [33.8] mg/dL), 265 (88.3%) underwent serial IVUS imaging in 537 arteries. At 52 weeks, mean change in percent atheroma volume was −2.13% with alirocumab vs −0.92% with placebo (difference, −1.21% [95% CI, −1.78% to −0.65%], $P < .001$). Mean change in maximum lipid core burden index within 4 mm was −79.42 with alirocumab vs −37.60 with placebo (difference, −41.24 [95% CI, −70.71 to −11.77]; $P = .006$). Mean change in minimal fibrous cap thickness was 62.67 µm with alirocumab vs 33.19 µm with placebo (difference, 29.65 µm [95% CI, 11.75-47.55]; $P = .001$). Adverse events occurred in 70.7% of patients treated with alirocumab vs 72.8% of patients receiving placebo.

Alirocumab PACMAN AMI

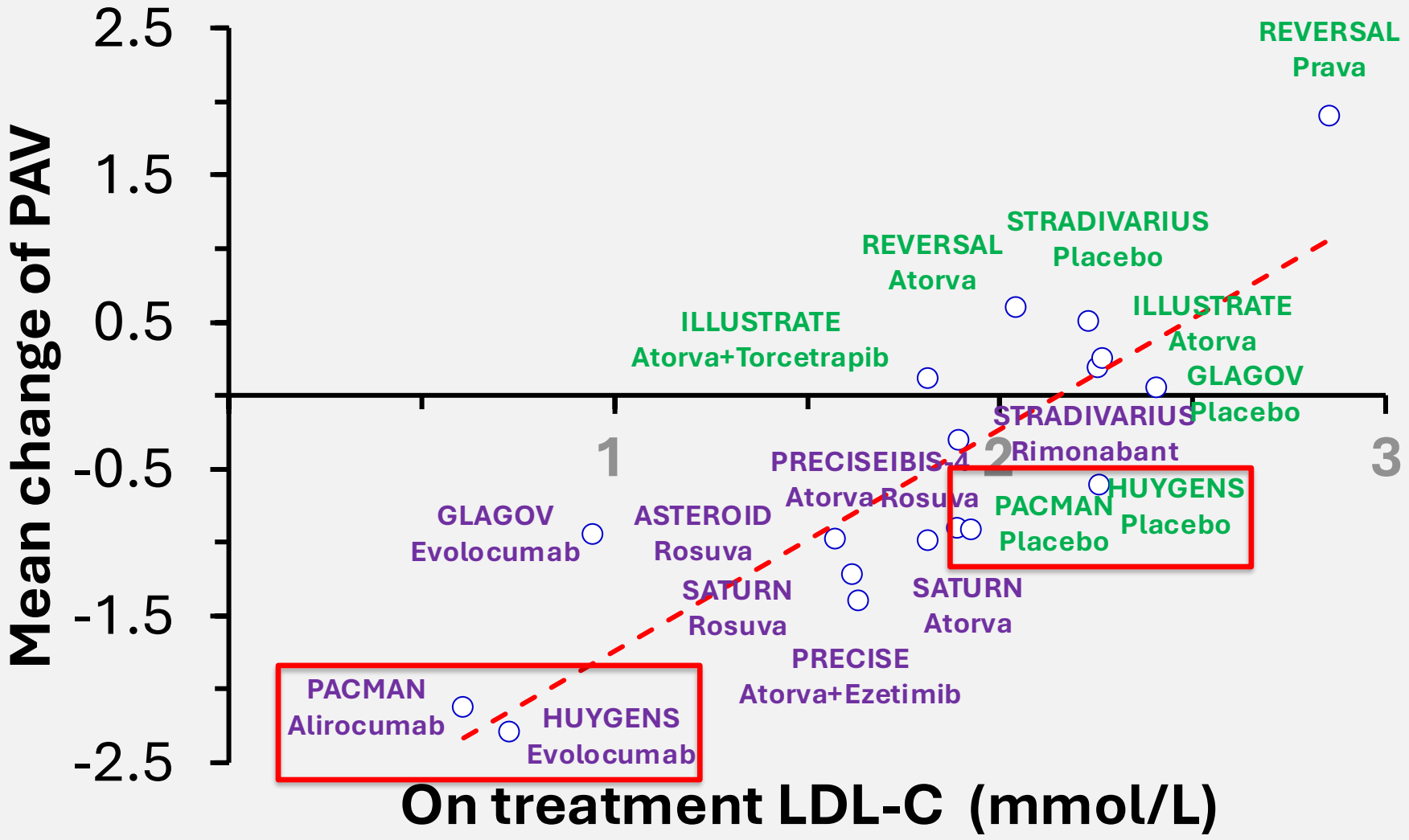
Conclusions

Compared with placebo, alirocumab initiated in the setting of acute AMI on top of high-intensity statin therapy resulted in greater decrease in PAV, larger reduction in lipid burden and higher increase in minimal fibrous cap thickness after 52 weeks of treatment.

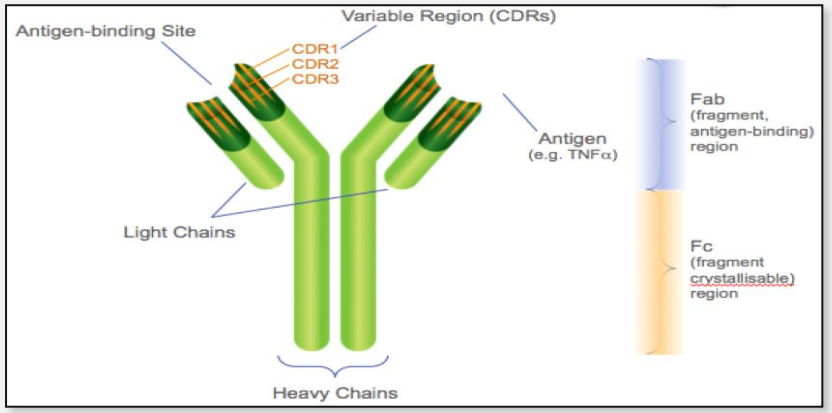
These findings indicate incremental coronary plaque regression, lipid core reduction and plaque stabilization with alirocumab and provide a mechanistic rationale in favor of early initiation of very intensive LDL-C lowering in acute MI patients.

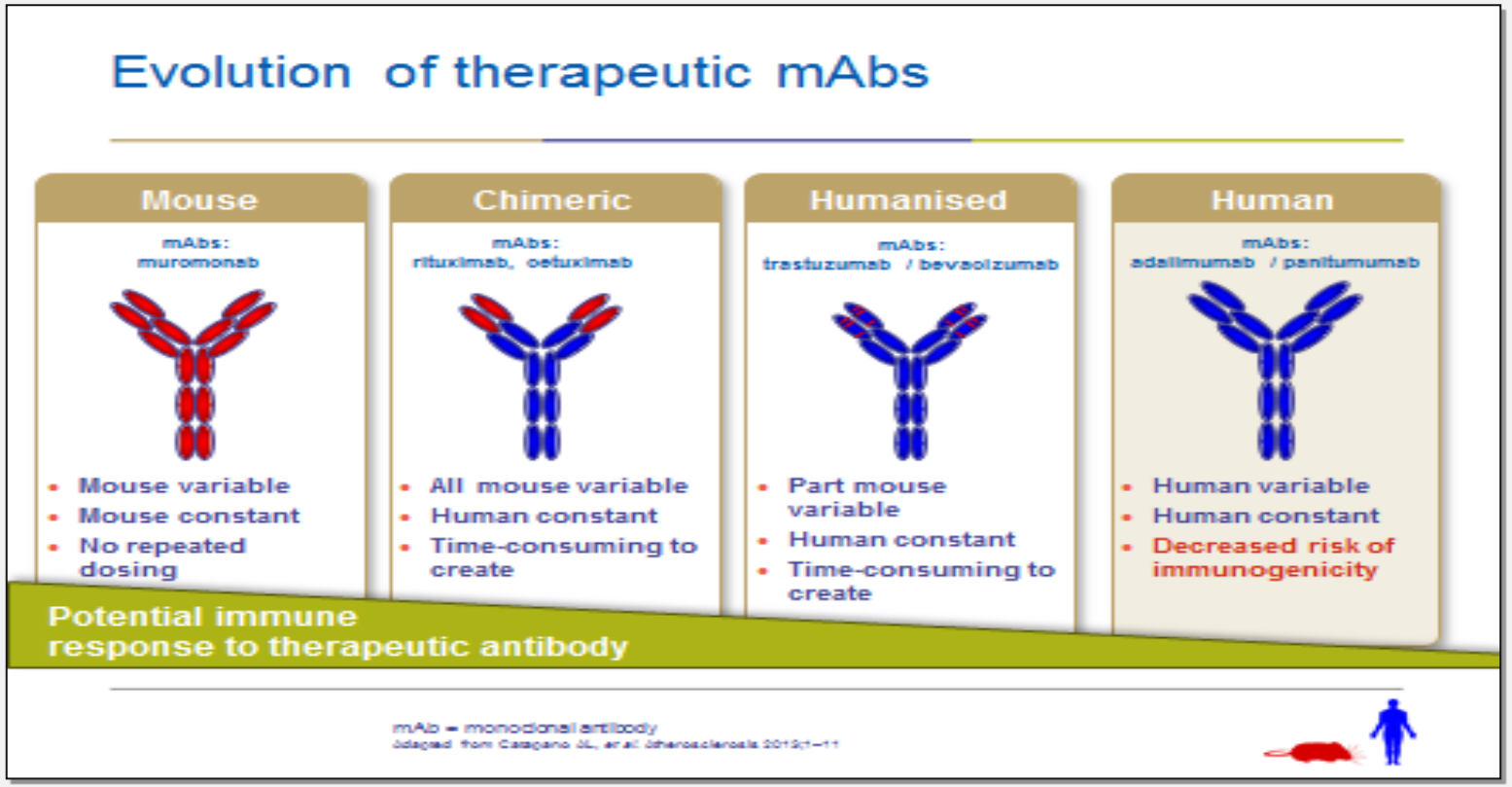
JAMA 2022;327:1771

Atherosclerosis plaque regression in serial IVUS studies



Monoclonal antibody





PCSK9 mAb (bococizumab) and CV events: SPIRE-1 and SPIRE-2 trials

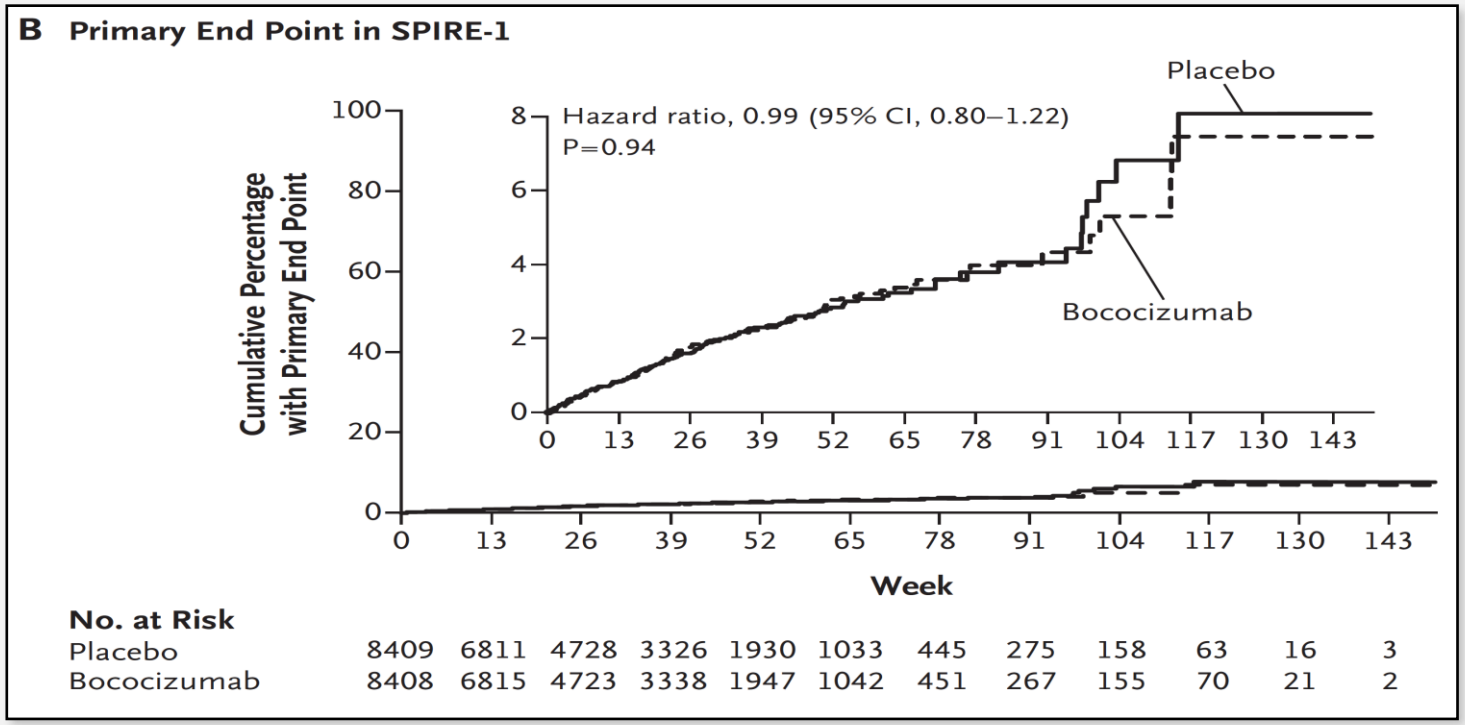
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients

P.M. Ridker, J. Revkin, P. Amarenco, R. Brunell, M. Curto, F. Civeira, M. Flather, R.J. Glynn, J. Gregoire, J.W. Jukema, Y. Karpov, J.J.P. Kastelein, W. Koenig, A. Lorenzatti, P. Manga, U. Masiukiewicz, M. Miller, A. Mosterd, J. Murin, J.C. Nicolau, S. Nissen, P. Ponikowski, R.D. Santos, P.F. Schwartz, H. Soran, H. White, R.S. Wright, M. Vrablik, C. Yunis, C.L. Shear, and J.-C. Tardif, for the SPIRE Cardiovascular Outcome Investigators*

New Engl J Med 2017;376:1527



PCSK9 mAb (bococizumab) and immunogenicity

New Engl J Med 2017;376:1517

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lipid-Reduction Variability and Antidrug-Antibody Formation with Bococizumab

Paul M Ridker, M.D., Jean-Claude Tardif, M.D., Pierre Amarenco, M.D., William Duggan, Ph.D., Robert J. Glynn, Sc.D., J. Wouter Jukema, M.D., John J.P. Kastelein, M.D., Albert M. Kim, M.D., Ph.D., Wolfgang Koenig, M.D., Steven Nissen, M.D., James Revkin, M.D., Lynda M. Rose, M.S., Raul D. Santos, M.D., Ph.D., Pamela F. Schwartz, Ph.D., Charles L. Shear, Dr.P.H., and Carla Yunis, M.D., for the SPIRE Investigators*

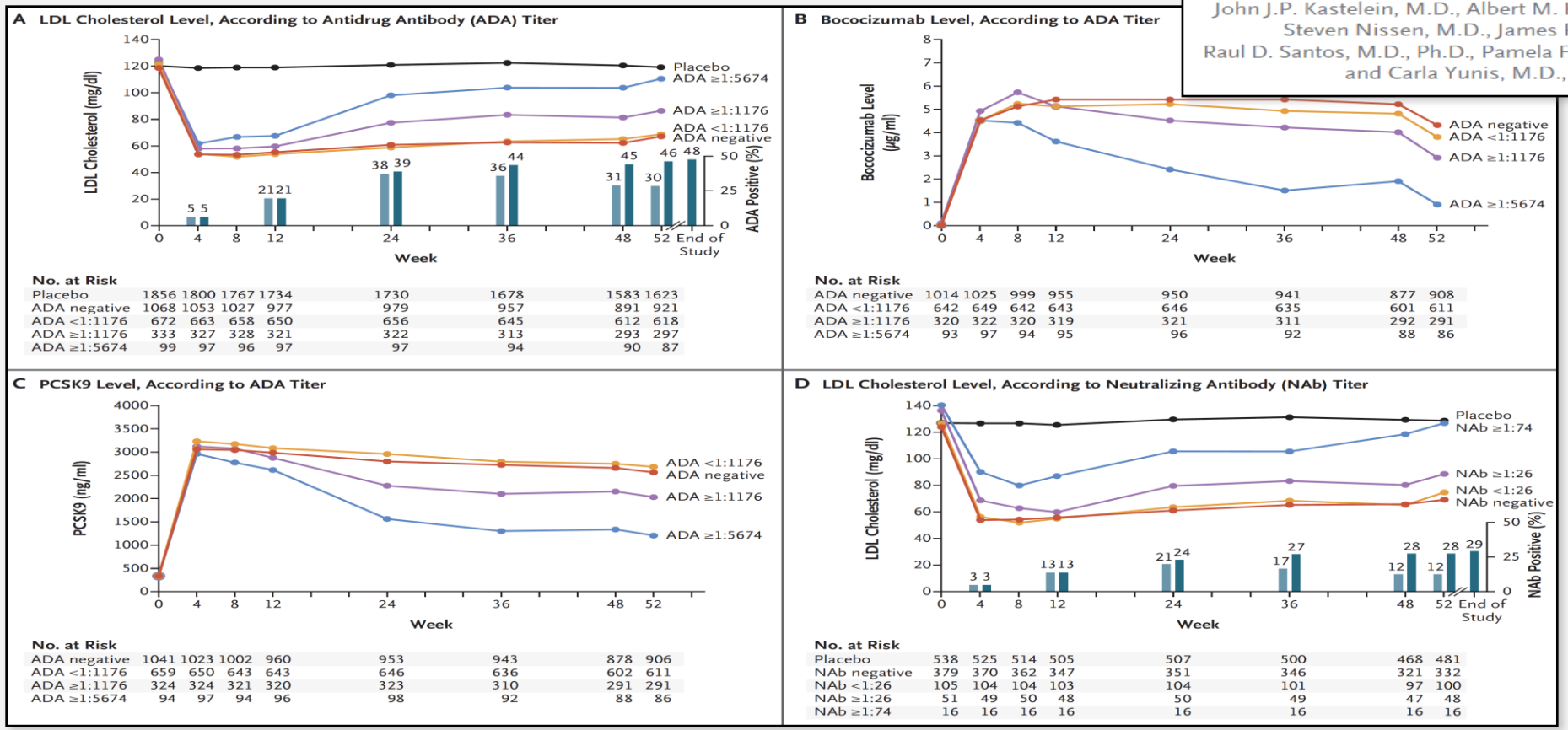
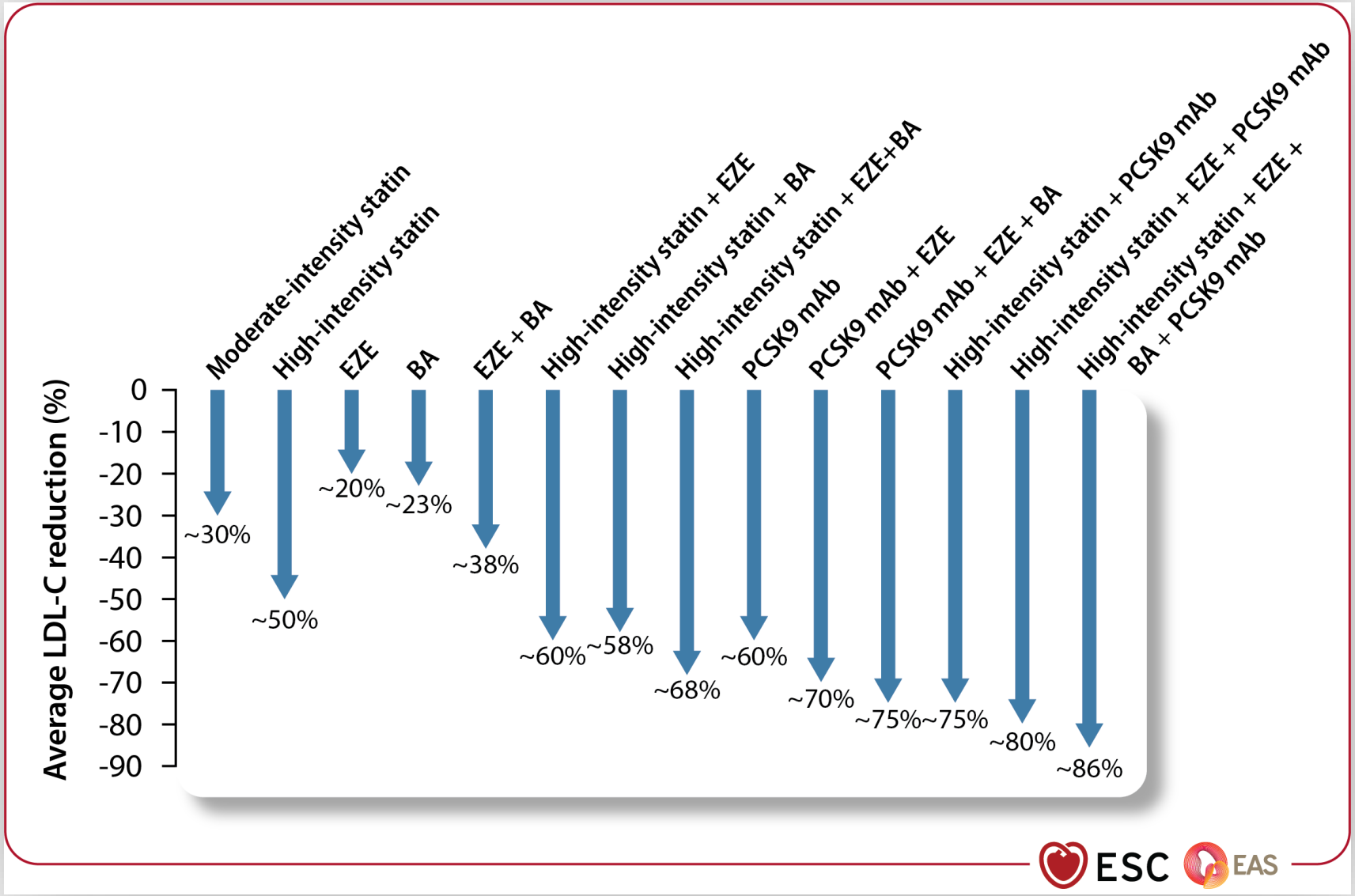
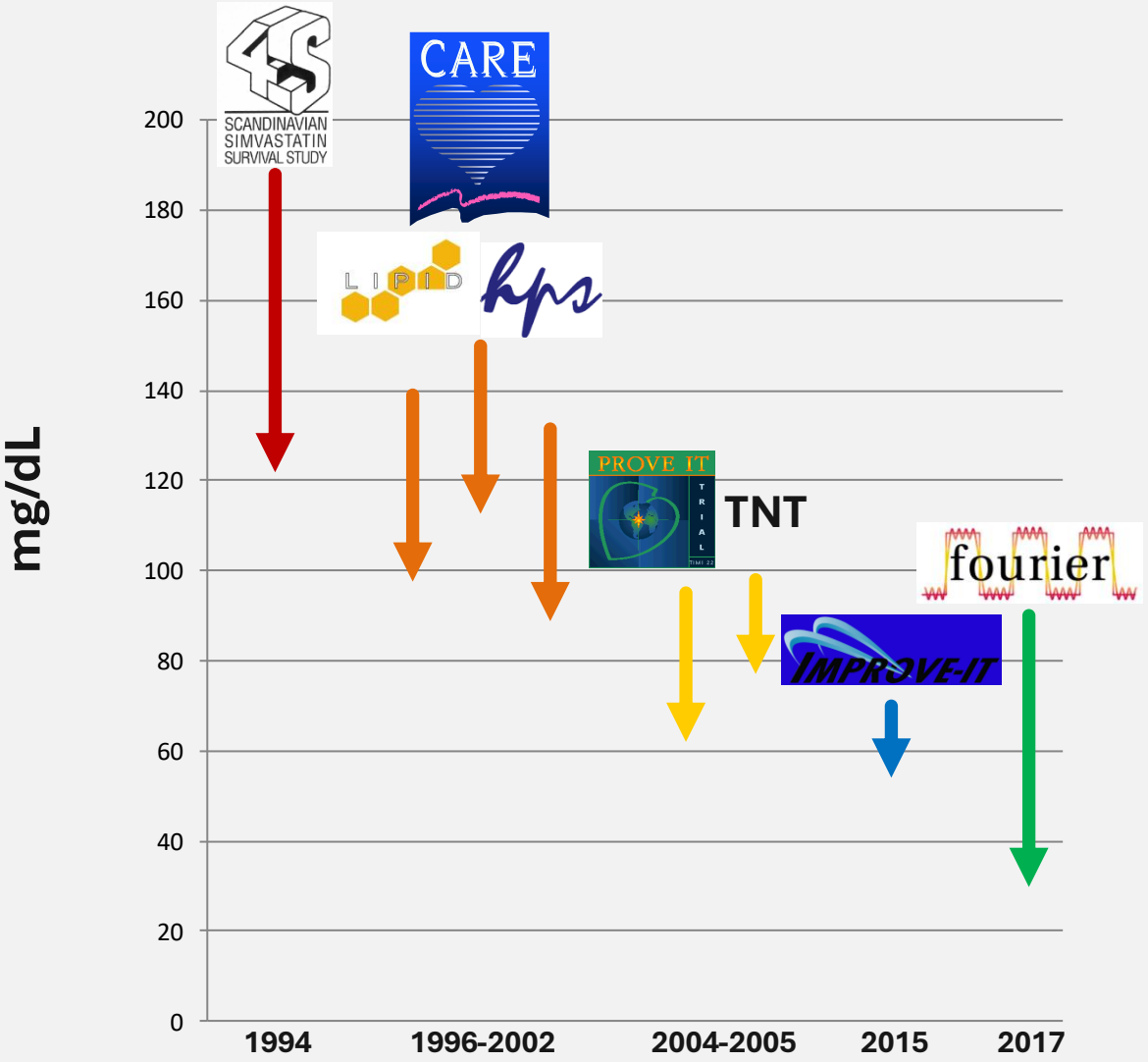


Figure 2

Average reduction in LDL-C levels with different pharmacological therapies with proven cardiovascular benefit.



A quarter of a century of treating LDL-C



High is bad

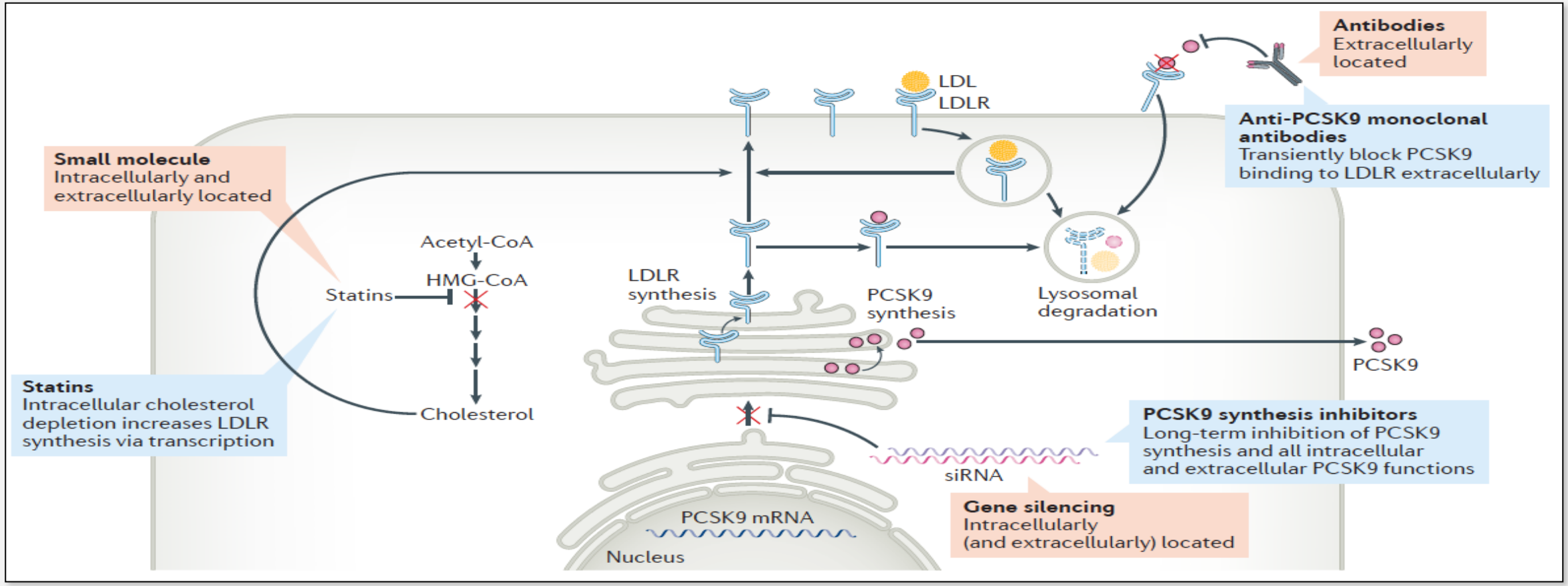
Average is not good

Lower is better

Even lower is even better

Lowest is best

Approaches to reduce LDL-C levels



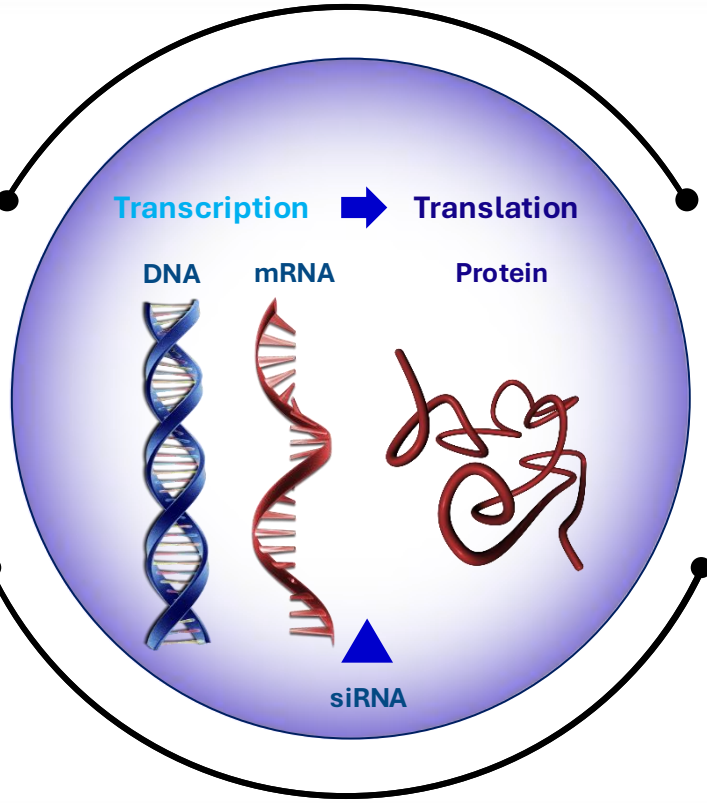
Nature Rev Cardiol 2018;15:261

Gene-Protein Synthesis

Non-coding RNAs

Only ~2% of the human genome encodes proteins while a significant portion codes for non-coding RNAs (ncRNAs)

Small interfering RNAs (siRNAs) are short double-stranded ncRNAs that function in gene silencing



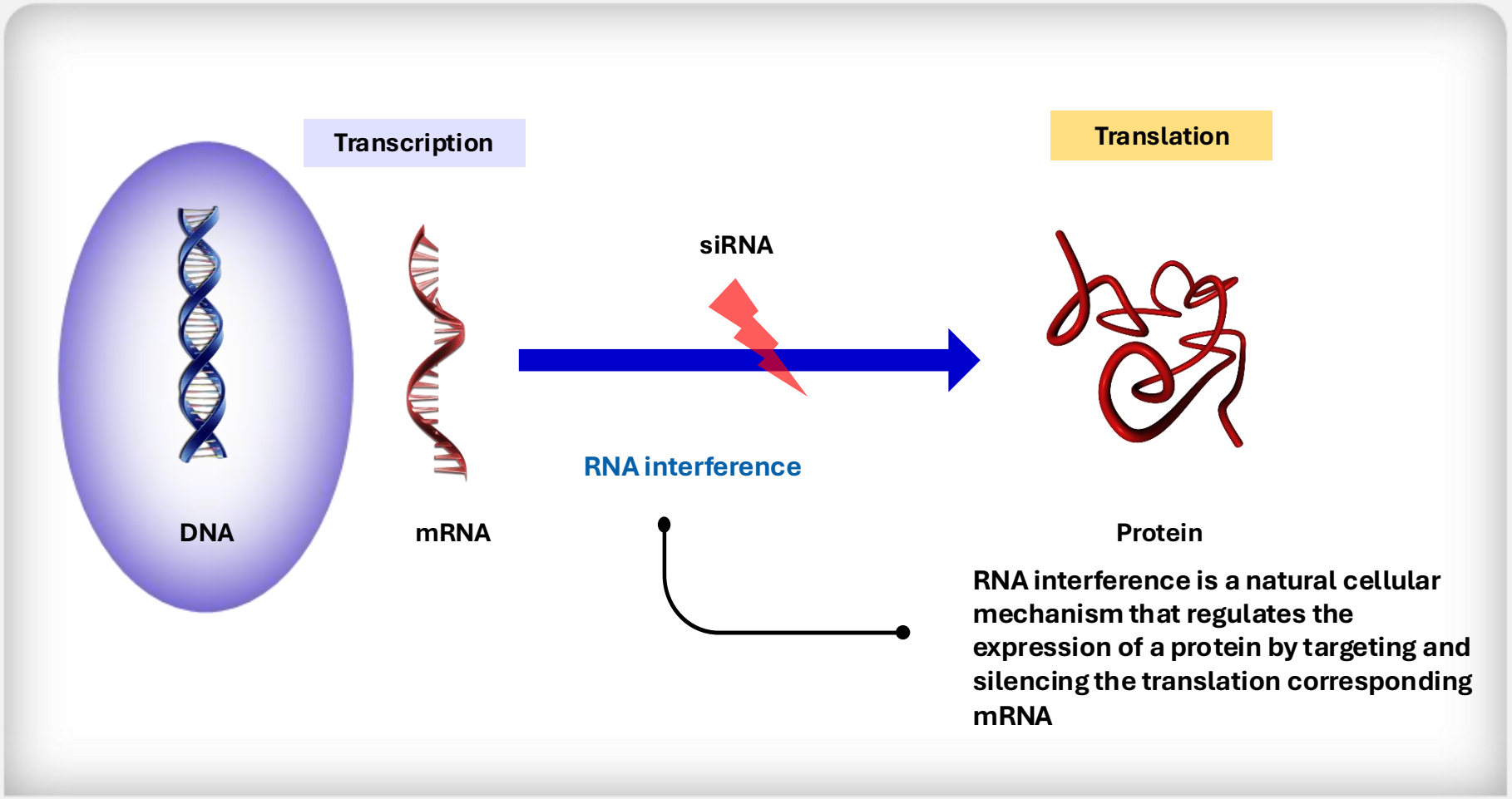
ncRNAs are involved in gene regulation, RNA maturation and protein synthesis

siRNAs prevent protein synthesis by degrading unique target mRNA through a natural mechanism called RNA interference

Reference 1
Reference 2
Reference 3
Reference 4
Reference 5

Gene-Protein Synthesis

RNA interference enables a cell to specifically shut down protein production



What is inclisiran ?

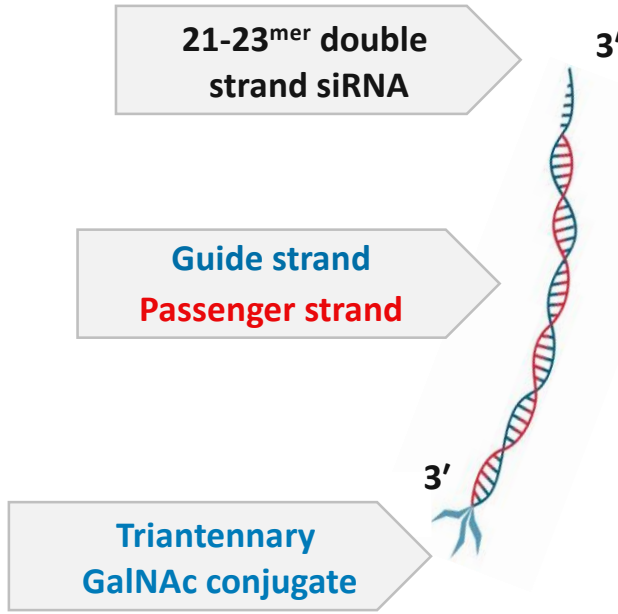
Small interfering RNA

- Synthetic small interfering RNA (siRNA) conjugated with triantennary GalNAc carbohydrate[1,2]
- Utilizes the natural RNA interference mechanism to degrade PCSK9 mRNA and prevent its translation to protein[2]

Chemical Modifications[3,4]

- 2′-fluoro and 2′-O-methyl modifications to **increase compound stability**
- Backbone phosphodiester linkages modified with phosphorothioates **to protect from degradation** by liver exonucleases
- Triantennary GalNAc conjugation for **targeted hepatic delivery**

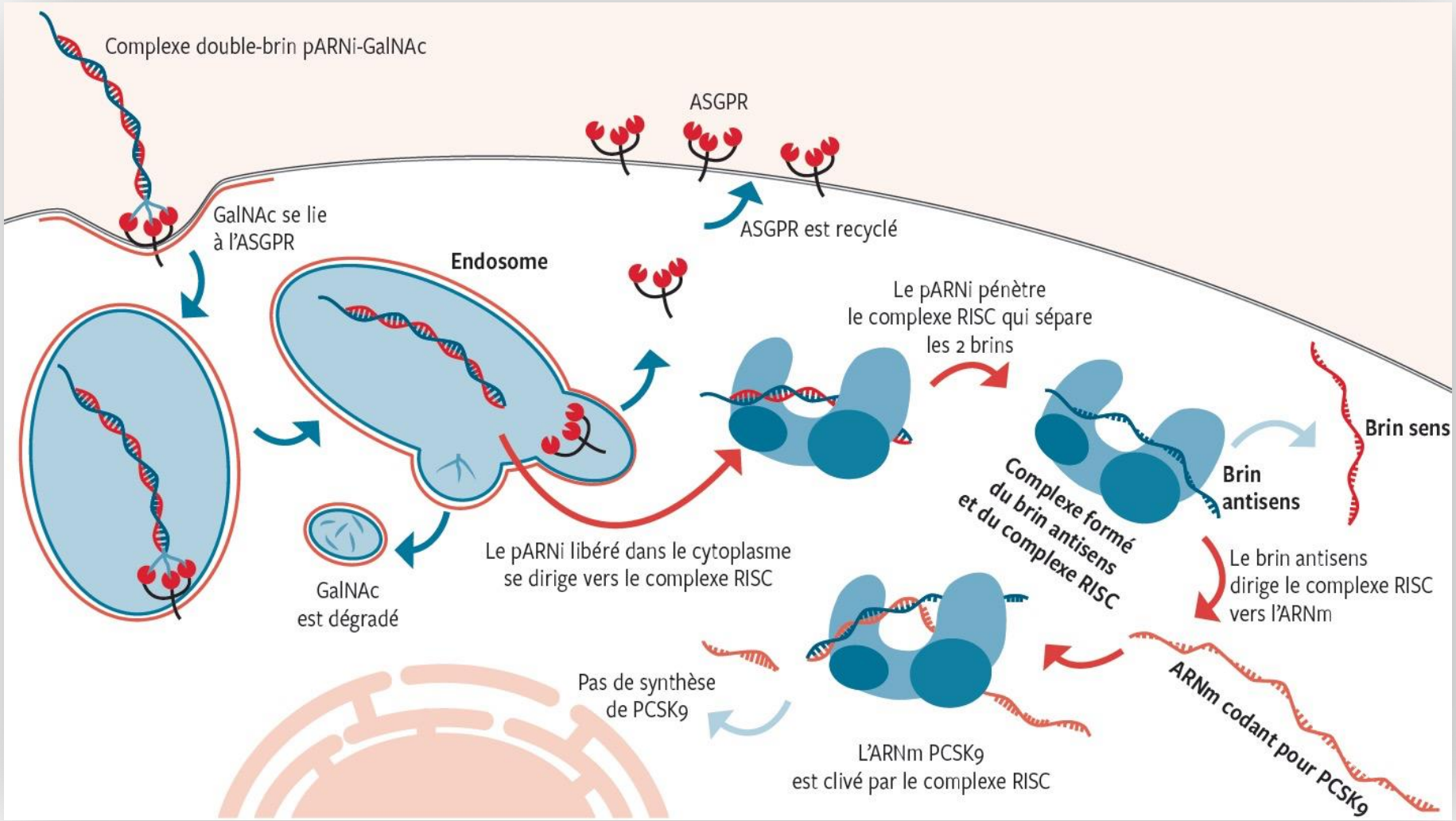
Inclisiran



[1]*Circ Res.* 2017;120:1063 [2]*N Engl J Med.* 2017;376:41
[3]Data on file. Inclisiran. Investigator's Brochure. Novartis Pharmaceuticals Corp; 2018 [4]*N Engl J Med.* 2017;376:4

Mechanism of action

GalNAc conjugation enables rapid uptake of inclisiran into hepatocytes via asialoglycoprotein receptor (ASGPR)



Rev Med Suisse 26 mai 2021;17(740):1039-46

Inclisiran treatment

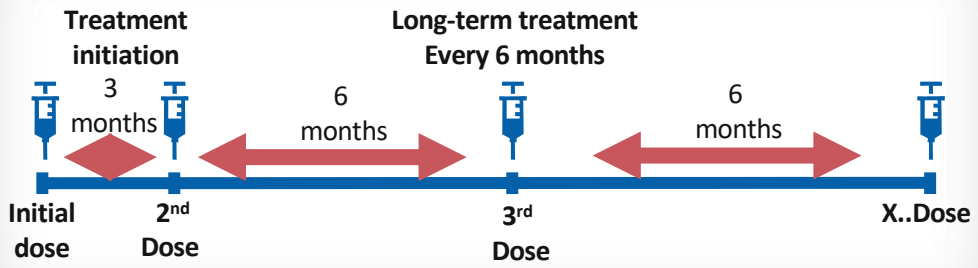
Dose & administration

Injection[1,2]

1.5 mL solution per syringe

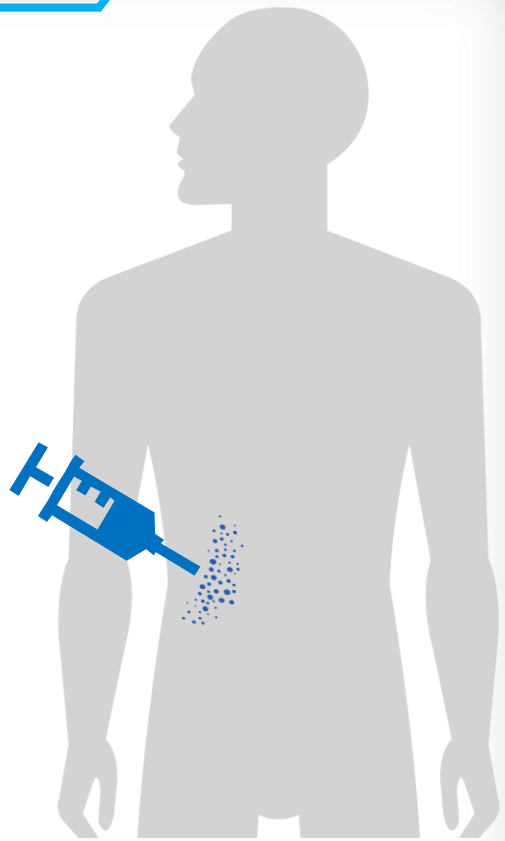
- 300 mg inclisiran sodium*
- Water as the diluent
- Sodium hydroxide and phosphoric acid (pH 7)
- Stored at room temperature

Dose regimen[1,2]



Administration[1,2]

Subcutaneous injection in the abdomen by healthcare professionals



[1]*Curr Pharm Des*. 2018;24:3622; [2]*N Engl J Med*. 2017;376:4

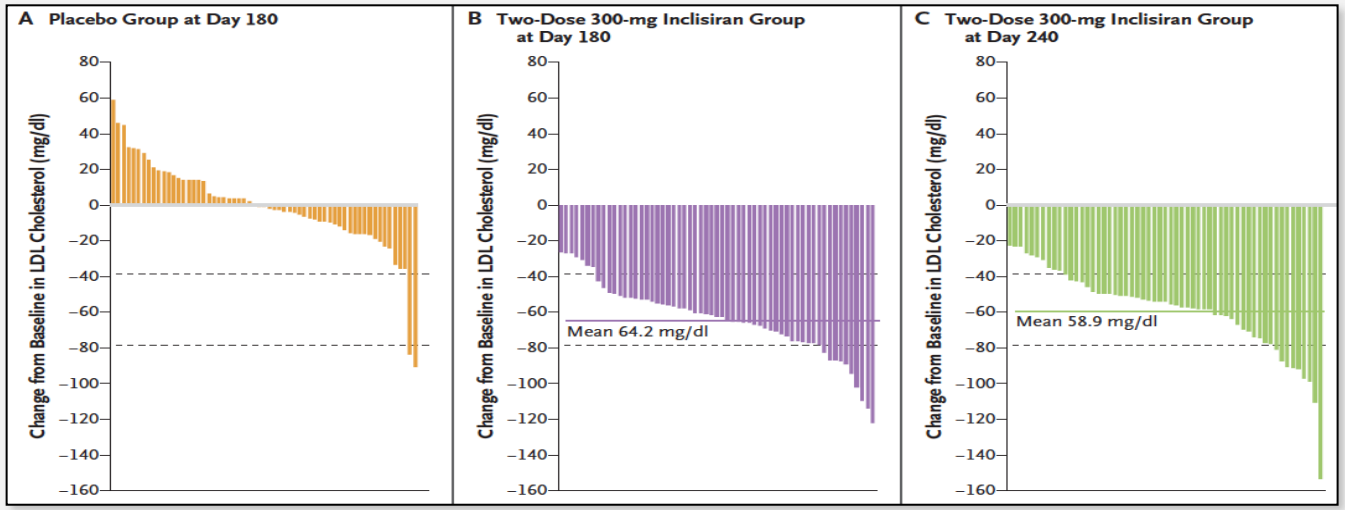
Lowering PCSK9 with siPCSK9

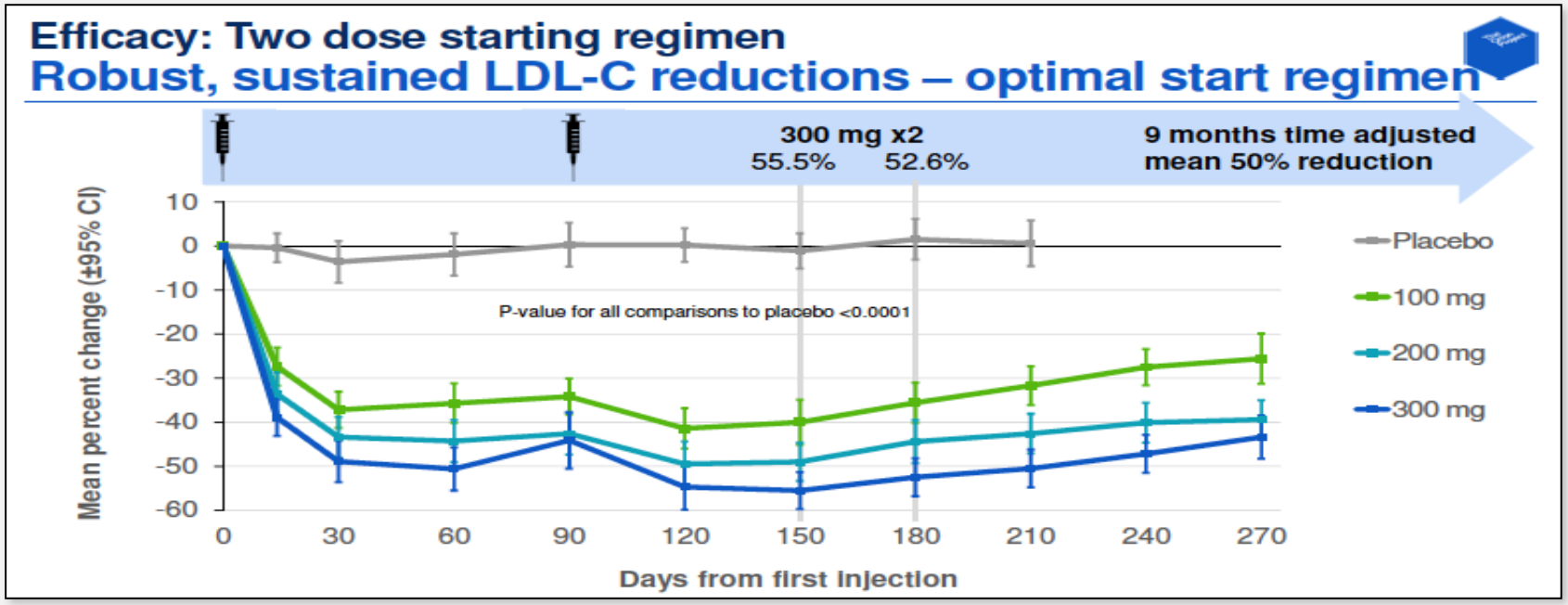
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.



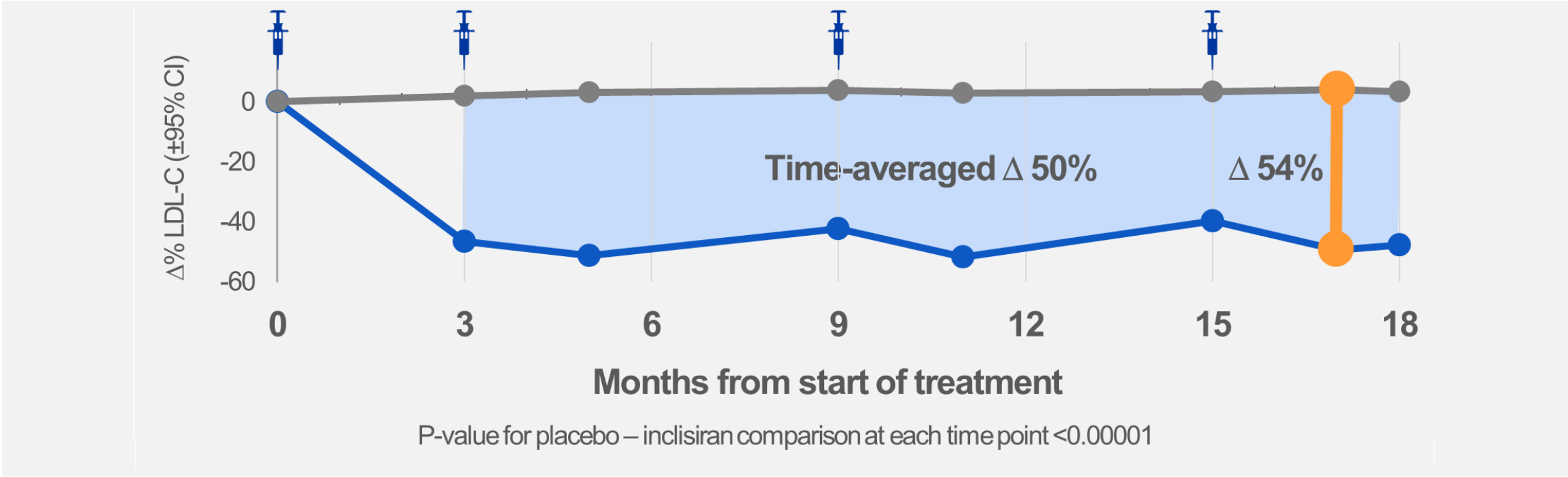


New Engl J Med 2017;376:1430

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

Percent change in LDL-C over time – observed values in ITT patients



1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

New Engl J Med 2020;382:1507

Inclisiran clinical studies

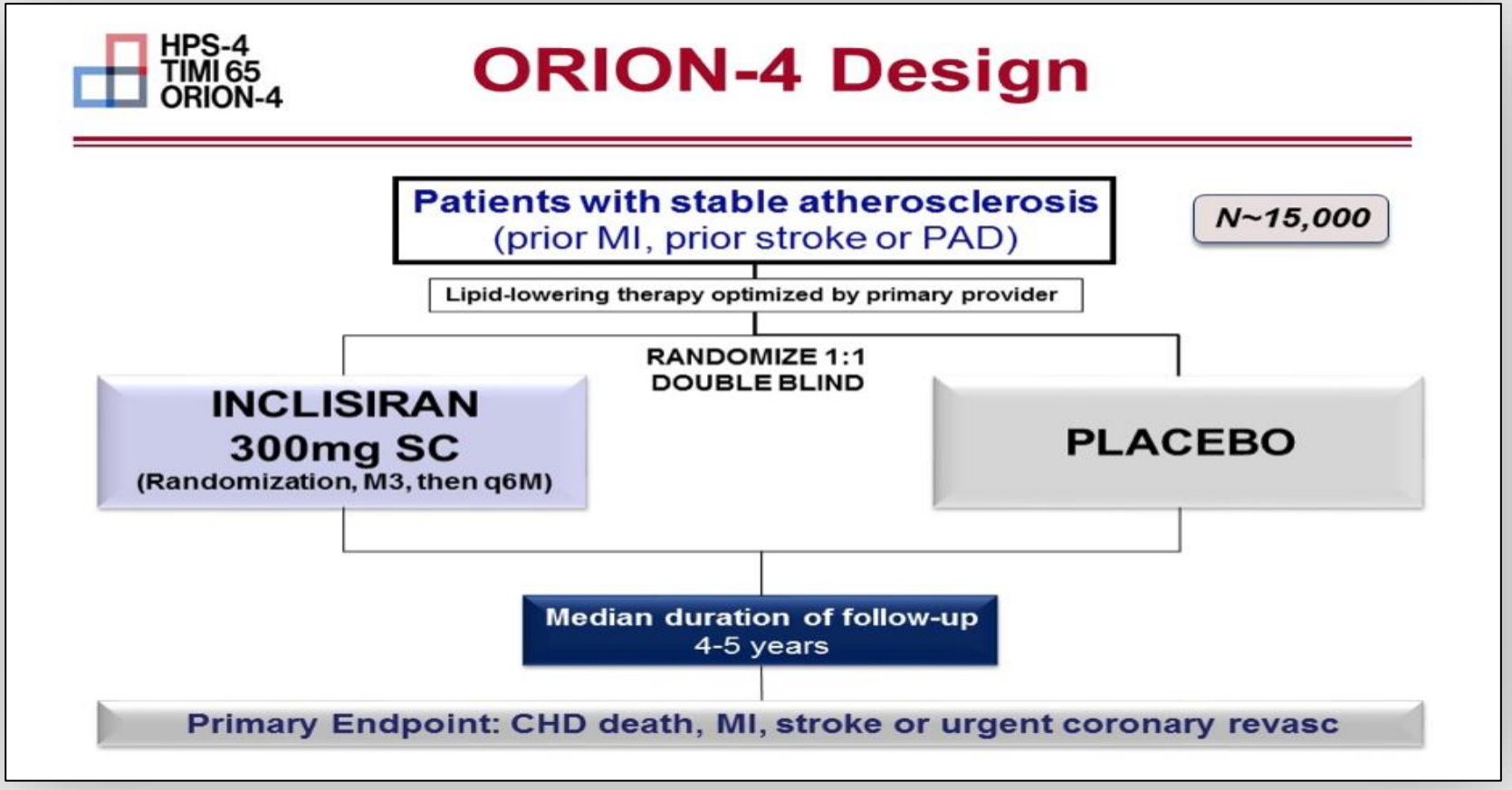
ORION development program

Étude	Phase clinique	Patients (N)	Population étudiée	Durée de suivi	Critère de jugement	Référence ClinicalTrials.gov
ORION-1	II	500	ASCVD ou ASCVD RE	180 jours	Baisse du LDL-C	NCT02597127[40]
ORION-2	II	4	HFHo	180 jours	Baisse du LDL-C	NCT02963311
ORION-3	II	490	ASCVD ~~or~~ ASCVD RE	48 mois	Baisse du LDL-C	NCT03060577
ORION-4	IIIb	15 000	ASCVD ~~or~~ ASCVD RE	60 mois	MACE	NCT03705234
ORION-5	III	45	HFHo	24 mois	Baisse du LDL-C	NCT03851705
ORION-6	I	24	Insuffisance hépatique	180 jours	Pharmacocinétique	NCT04765657
ORION-7	I	31	Insuffisance rénale	60 jours	Pharmacocinétique	NCT03159416[40]
ORION-8	III	3700	ASCVD ~~or~~ ASCVD RE ~~or~~ HFHe/HFHo	36 mois	Baisse du LDL-C	NCT03814187
ORION-9	III	482	HFHe	18 mois	Baisse du LDL-C	NCT03814187
ORION-10	III	1561	ASCVD	18 mois	Baisse du LDL-C	NCT03399370[17]
ORION-11	III	1617	ASCVD ~~or~~ ASCVD RE	18 mois	Baisse du LDL-C	NCT03400800[17]
ORION-12	I	48	Population saine	180 jours	QT et ECG	–
ORION-13	III	12	HFHo chez l'adolescent (de 12 à < 18 ans)	24 mois	Baisse du LDL-C	NCT04659863
ORION-14	I	40	Étude de recherche de dose	–	Baisse du LDL-C	NCT04774003
ORION-15	II	308	Étude de recherche de dose, ASCVD	270 jours	Baisse du LDL-C	NCT04666298
ORION-16	III	150	HFHe chez l'adolescent (de 12 à < 18 ans)	24 mois	Baisse du LDL-C	NCT04652726

Rev Med Suisse 26 mai 2021;17(740):1039-46

Opportunities and challenges for the future

Efficacy of different approaches to lipid lowering



The modern concept of lipid-lowering strategies to reduce cardiovascular diseases

ARN: du prix Nobel au traitement, la cardiologie au-devant de la scène

Pr FRANÇOIS MACH et Pr OLIVIER MULLER

Rev Med Suisse 26 mai 2021;17(740):1007-8

Une baisse du cholestérol LDL de longue durée: enfin le silence

MAËLLE ACHARD[a], ALIKI BUHAYER[b], KEVIN DOBRETZ[a], Pr GEORG EHRET[a], Pr FRANÇOIS MACH[a]

Rev Med Suisse 26 mai 2021;17(740):1039-46

Atherosclerosis 368 (2023) 14–24

Contents lists available at ScienceDirect

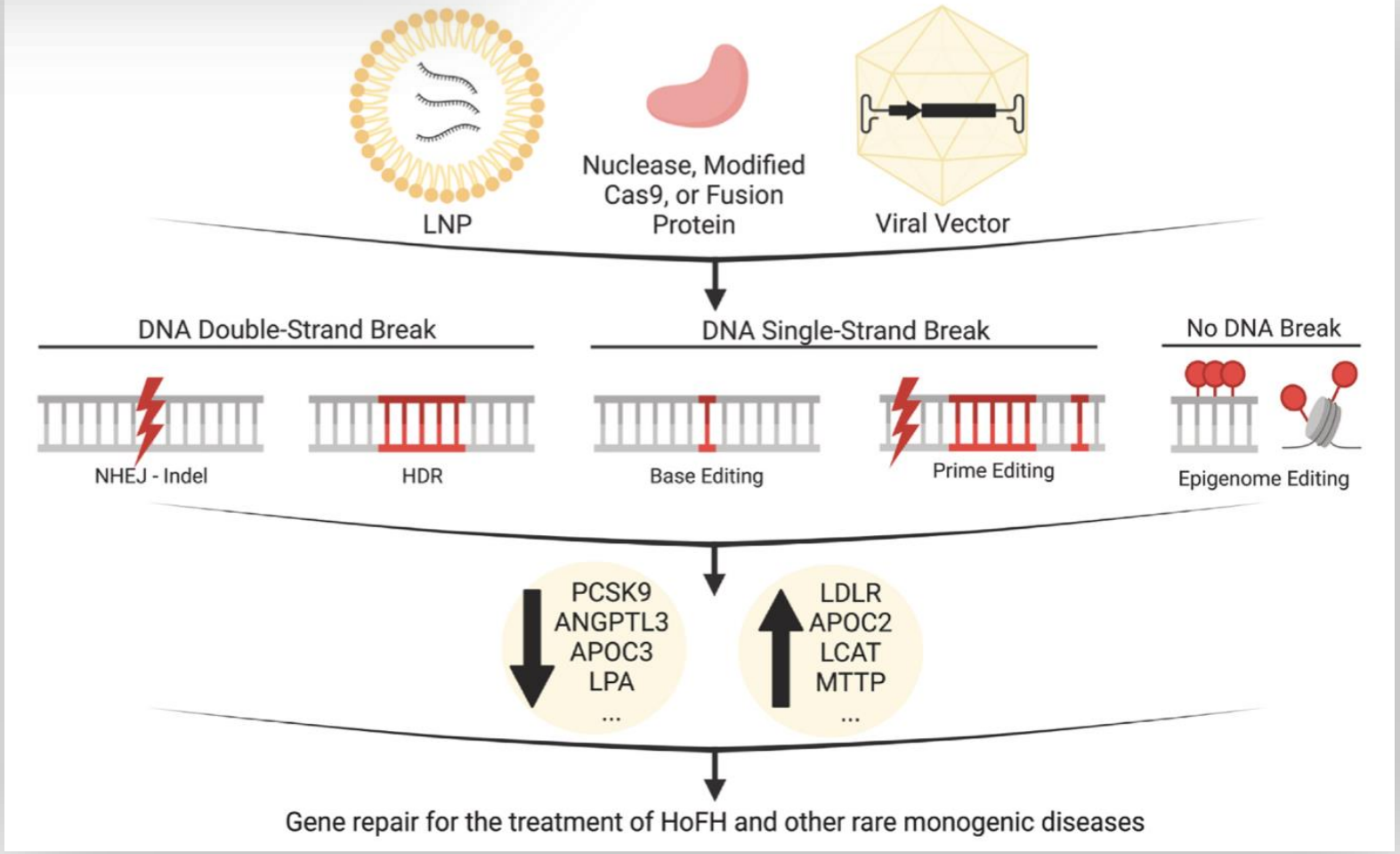
Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Gene editing for dyslipidemias: New tools to “cut” lipids

Sylvia Stankov, Marina Cuchel *



Conclusions/Messages

Athérosclérose 12-1-2026

LDL-C has <u>both</u> a causal and a cumulative effect on CHD risk

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jacc.2015.02.020

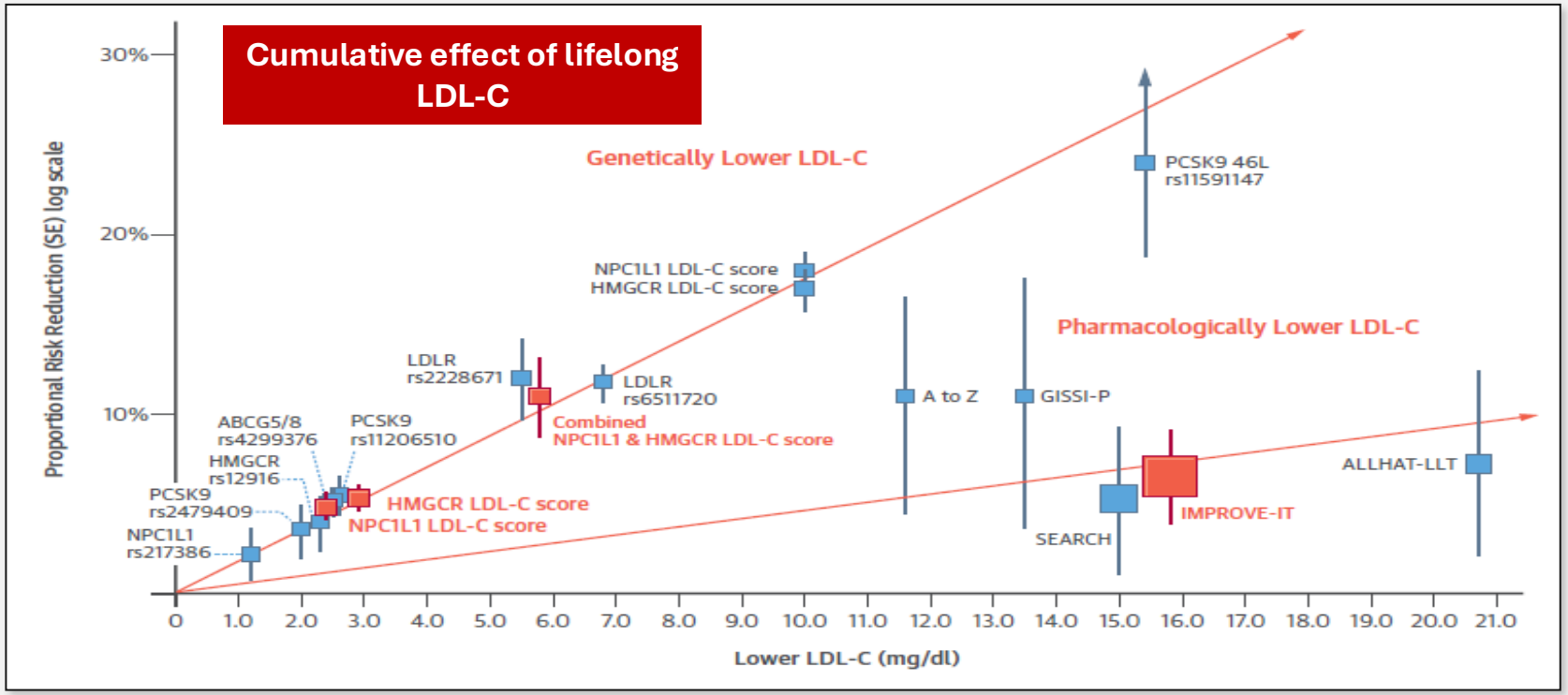
Effect of Naturally Random Allocation to Lower Low-Density Lipoprotein Cholesterol on the Risk of Coronary Heart Disease Mediated by Polymorphisms in *NPC1L1*, *HMGCR*, or Both

A 2 × 2 Factorial Mendelian Randomization Study

Brian A. Ference, MD, MPhil, MSc,*†‡ Faisal Majeed, MBBS,* Raju Penumetcha, MD,‡ John M. Flack, MD, MPH,*‡ Robert D. Brook, MD§

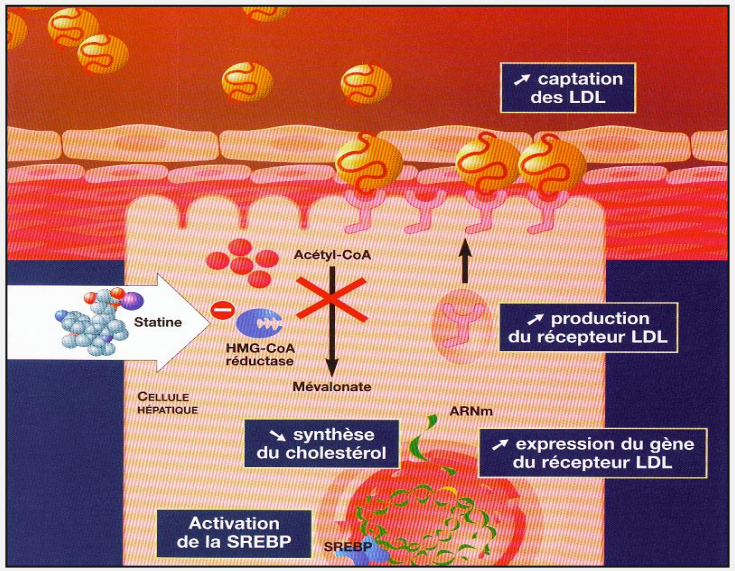
Meta-analysis on > 320’000 pts:

- Each mmol/L of LDL-C reduction is associated with a significant reduction of coronary events

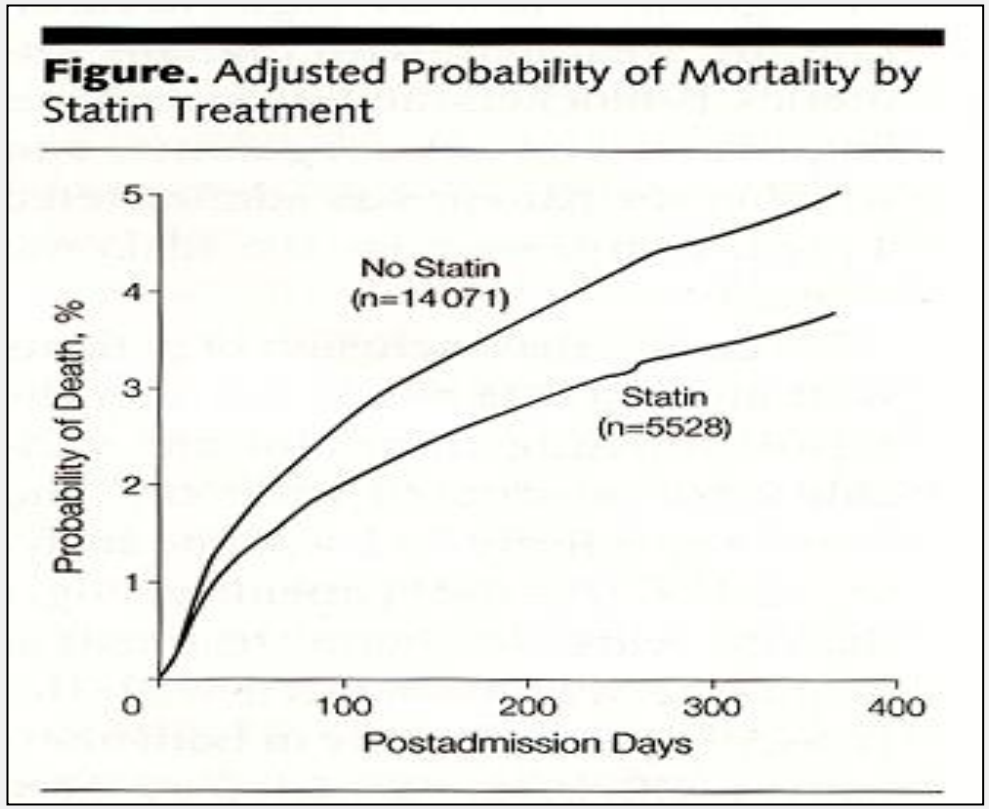


Conclusions/Messages

Les statines (inhibiteurs de l'HMG-CoA synthase) diminuent la synthèse cellulaire de cholésterol et le taux sanguin de LDL.

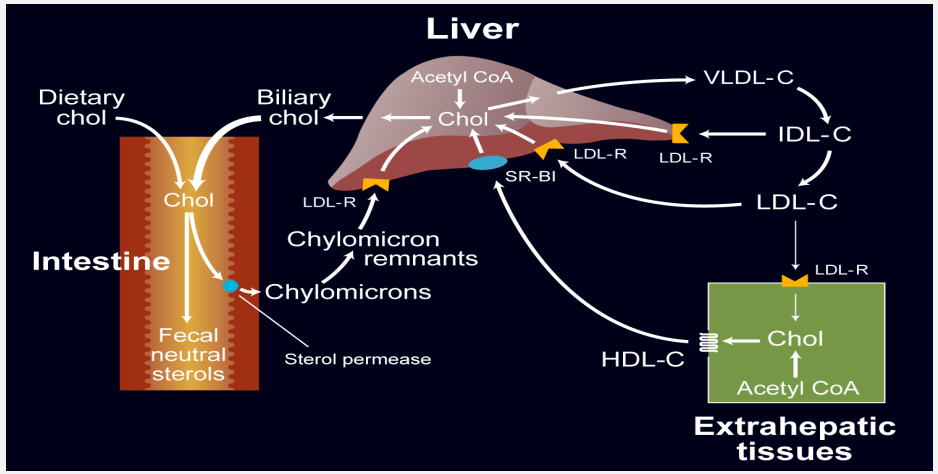


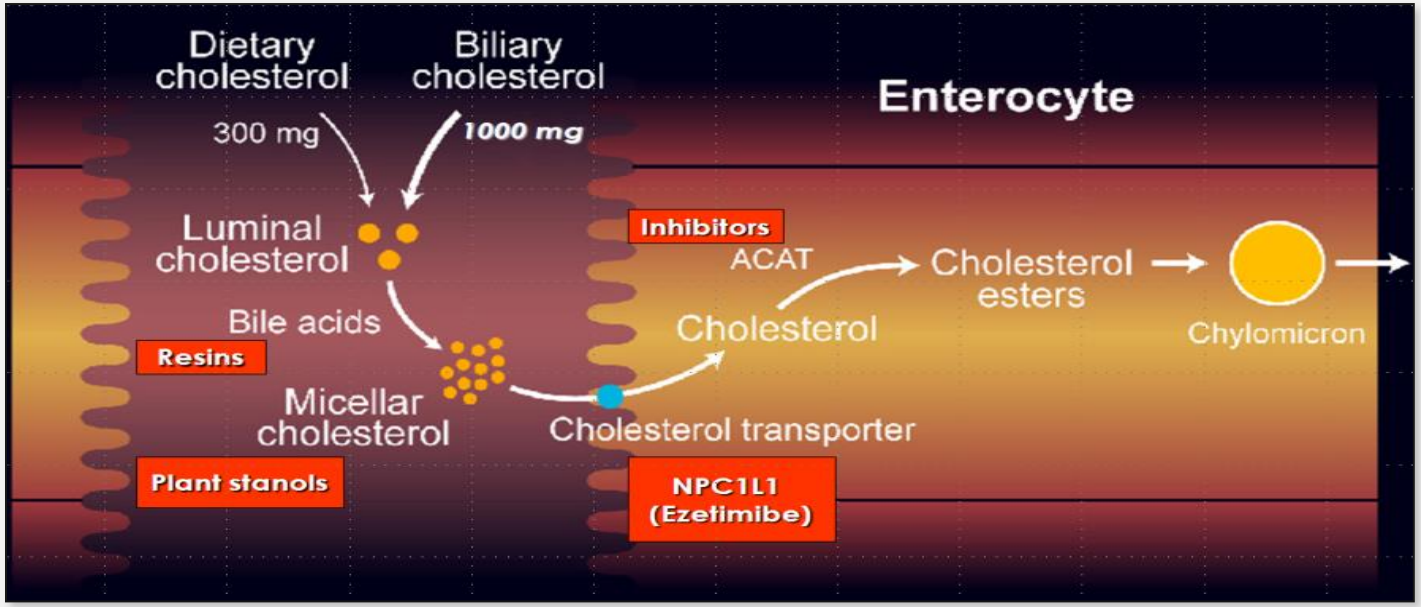
Une réduction des événements et de la mortalité cardiovasculaire.



Conclusions/Messages

Une diminution de l'absorption intestinal de cholésterol (ezetimibe) permet d'augmenter l'effet hypolipémiant des statines.





Conclusions/Messages

Une diminution de l'activité de PCSK9 (via un anticorps) diminue très largement le LDL, même en addition à un traitement de statine, ainsi que le risque de futurs événements cardiovasculaires