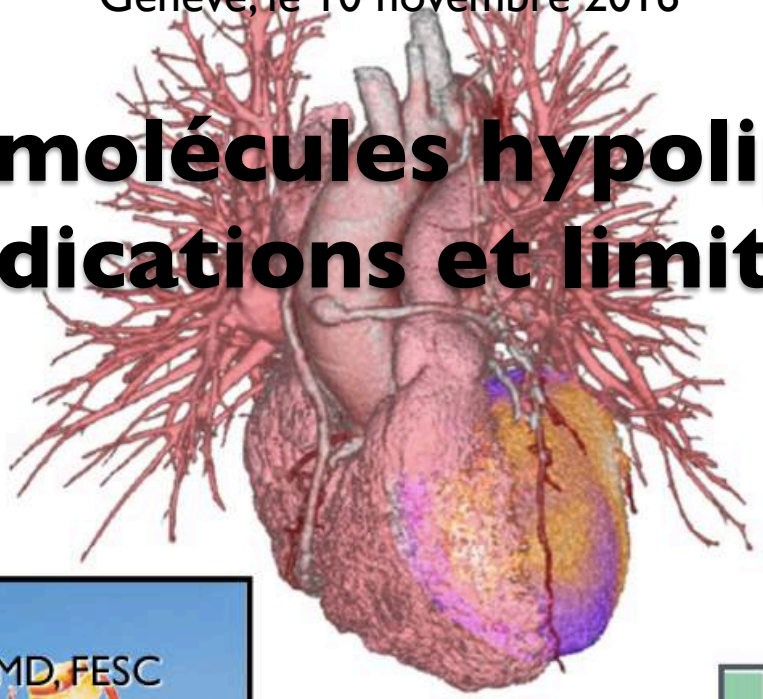
Formation continue de l'Association genevoise de Médecins travaillant en Réseau REMED
Genève, le 10 novembre 2016

Nouvelles molécules hypolipémiantes: Indications et limites



Service de Cardiologie

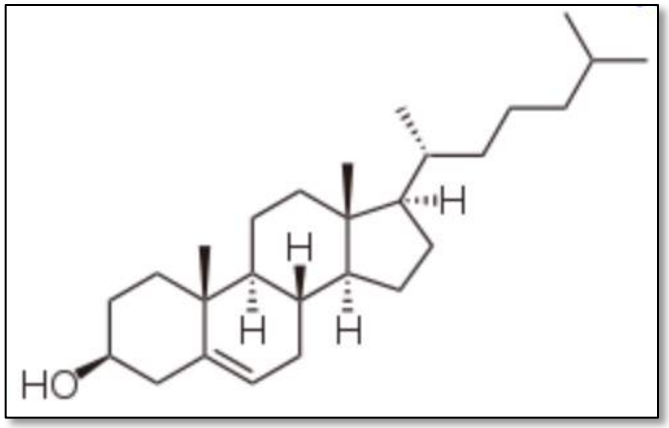
HUG Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Liens d'intérêts

Reçu des honoraires pour conférences et advisory board de:

Amgen, Astra-Zeneca, BMS, Daiichi-Sankyo, MSD, Pfizer et Sanofi.



Exposé

- Cholestérol/ Statine/ Ezetrol
- Les inhibiteurs de PCSK9
- Un dessert, salé...

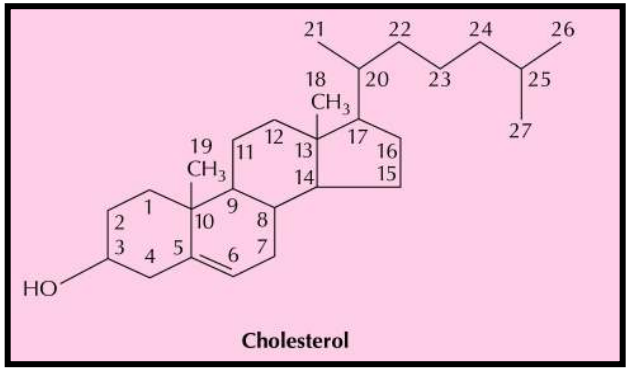
Cholestérol

***Chole:* bile** ***Stereos:* solide**

Fait partie des substances fondamentales de l'organisme et est un composant de tous les tissus

Le cholestérol est important en tant que:

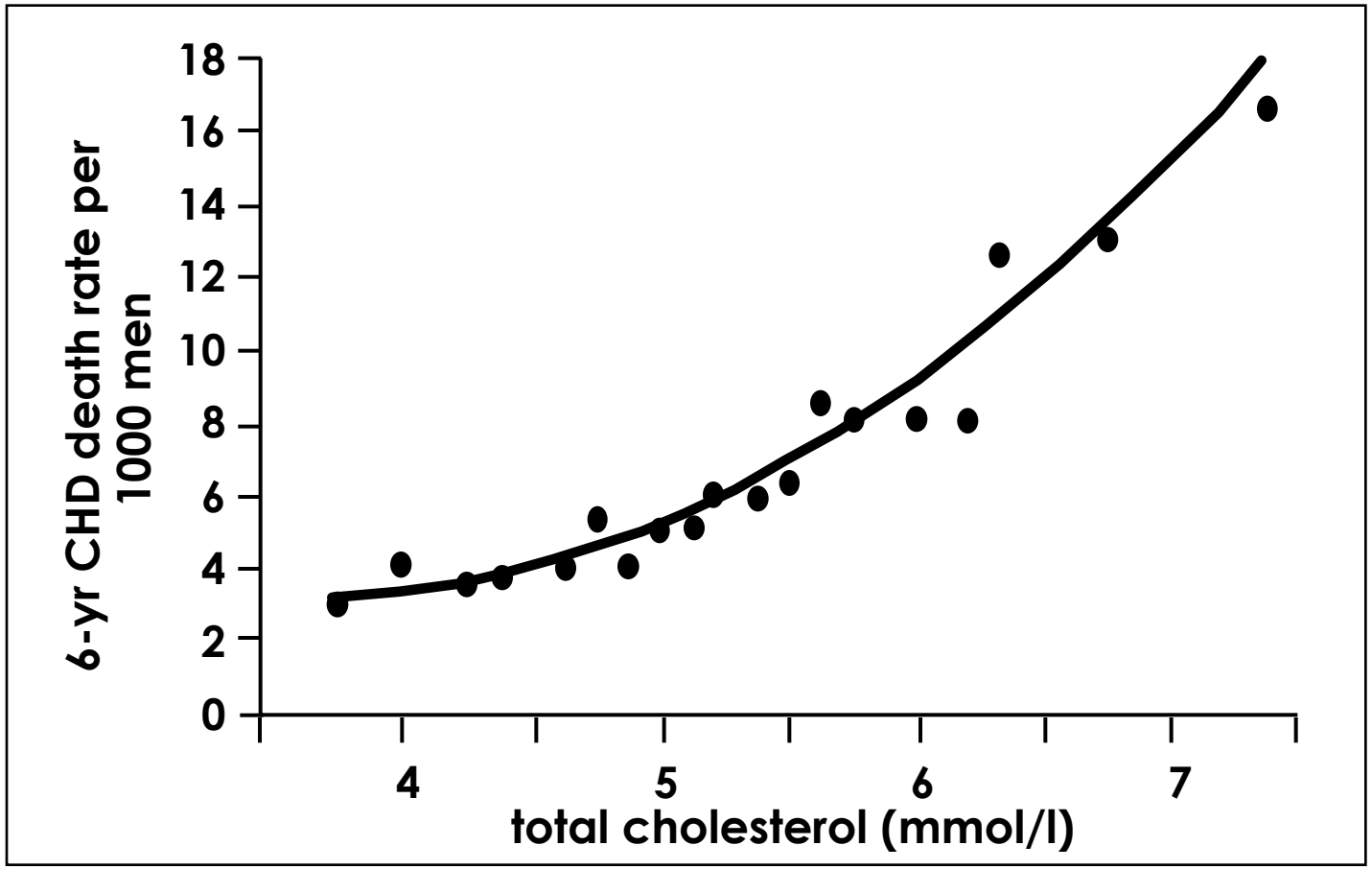
- Elément de la membrane cellulaire
- Substance de base pour:
  - les acides biliaires (digestion de certains aliments)
  - vitamine D (formation des os)
  - hormones (oestrogènes et testostérone)



Cholesterol

Cholestérol et et Risque Cardiovasculaire

MRFIT: Age-Adjusted CHD Death Rate
and Serum Cholesterol in 361,662 US Men



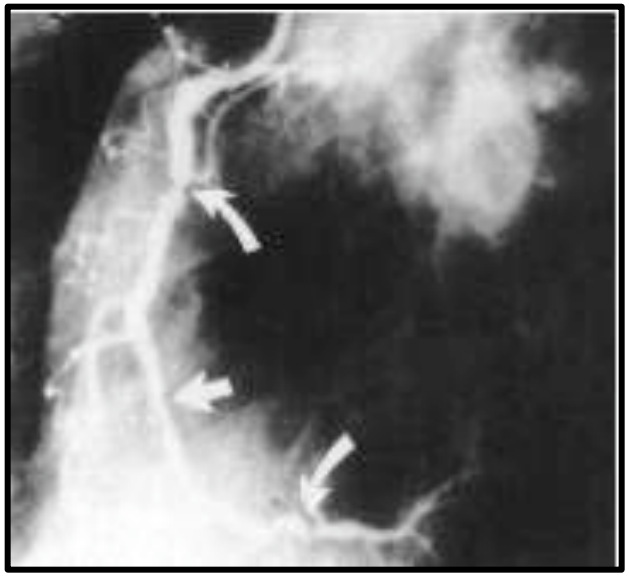
Lancet 1986;2:933

Cholestérol et athérosclérose

Homozygous familial hypercholesterolaemia is characterised by very high LDL cholesterol concentrations (usually >13 mmol/L), cutaneous and tendinous xanthomata, and early cardiovascular disease, and untreated patients rarely survive beyond the age of 30 years.

Relation of Cholesterol-Year Score to Severity of Calcific Atherosclerosis and Tissue Deposition in Homozygous Familial Hypercholesterolemia

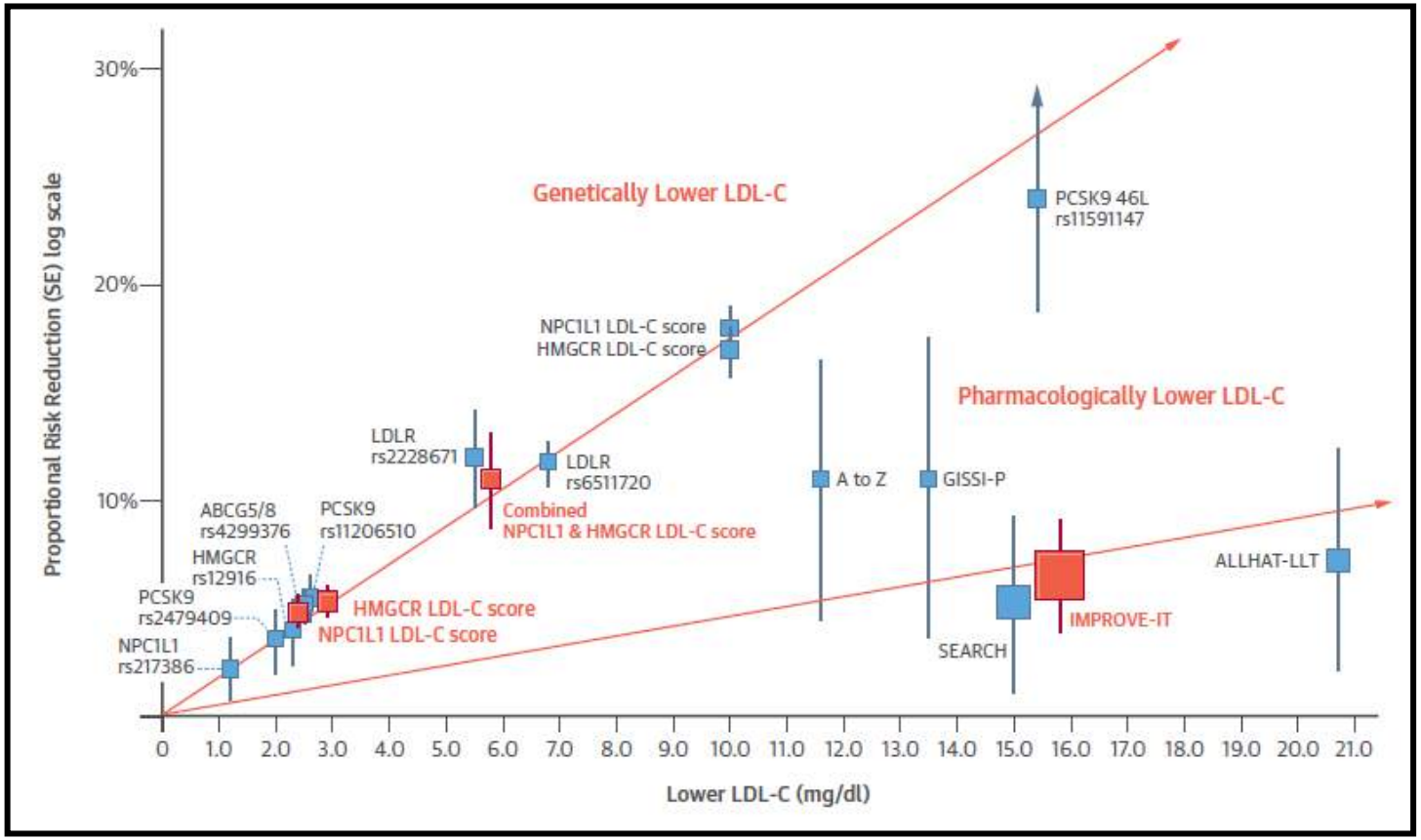
Hartmut H.-J. Schmidt, MD, Suvimol Hill, MD, Erini V. Makariou, MD, Irwin M. Feuerstein, MD, Klaus A. Dugi, MD, and Jeffrey M. Hoeg, MD



La preuve génétique: le LDL-c est un facteur de risque cardiovasculaire

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



JACC 2015;65:1552-61

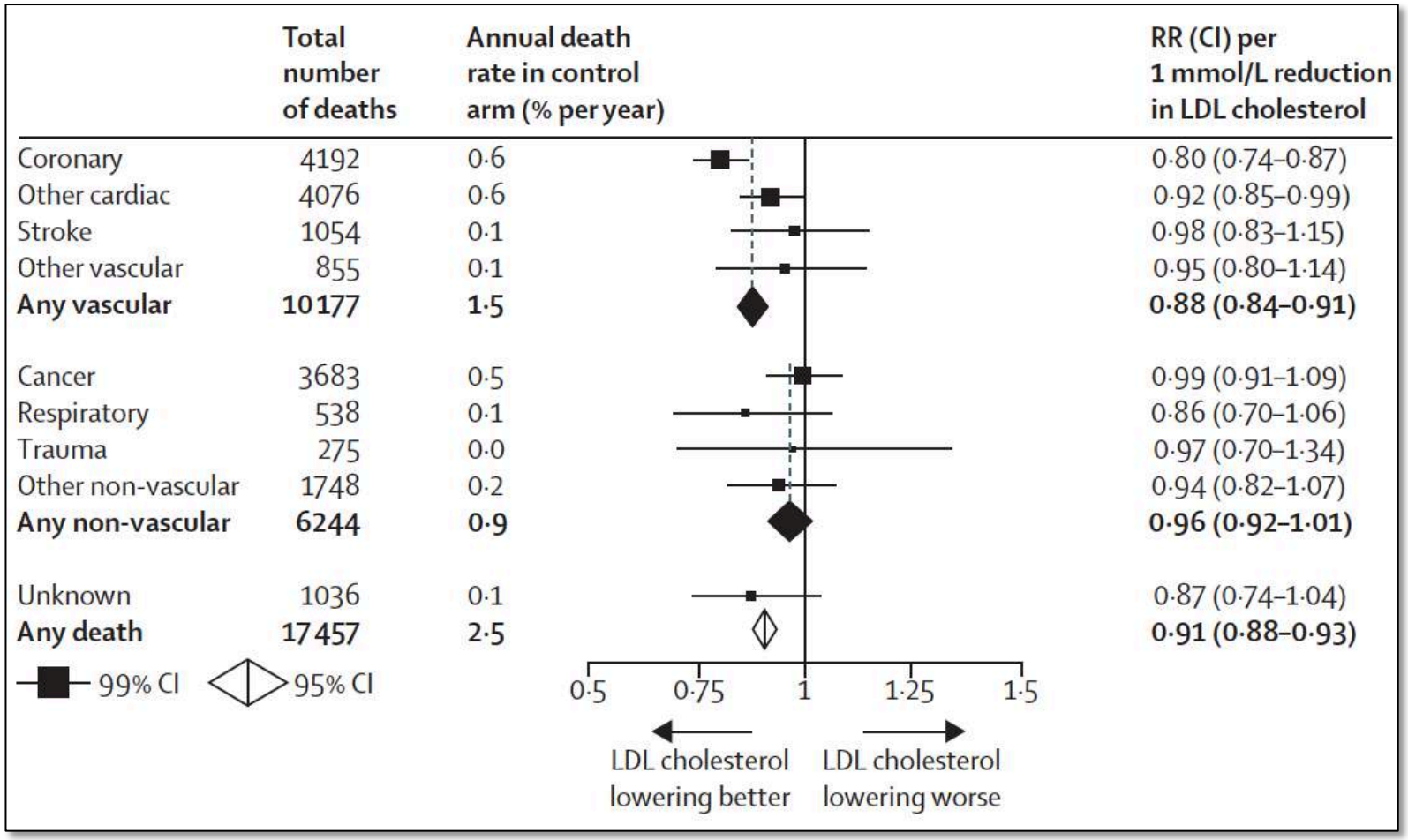
Statines – les évidences

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

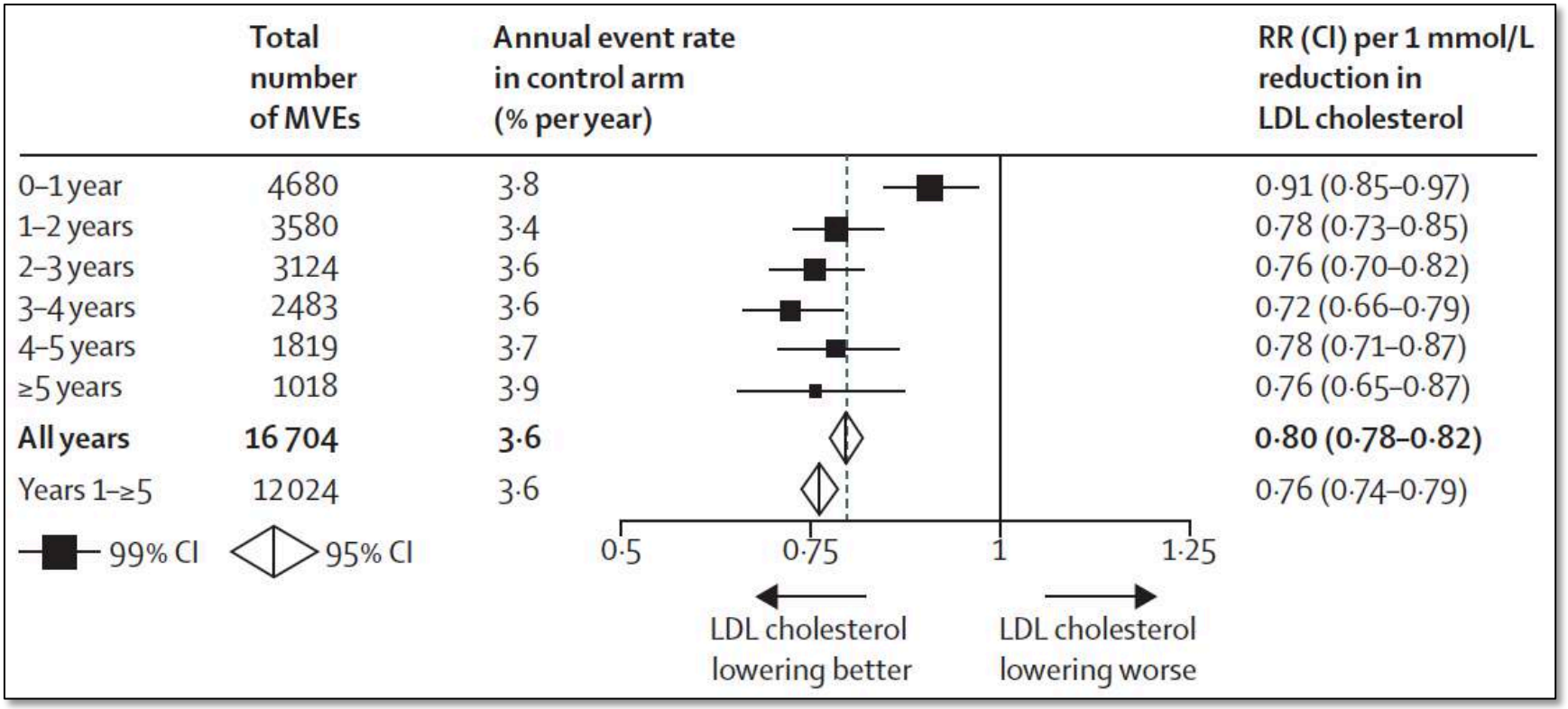
The Lancet September 8th, 2016
30 pages, 309 references

Statines – les évidences



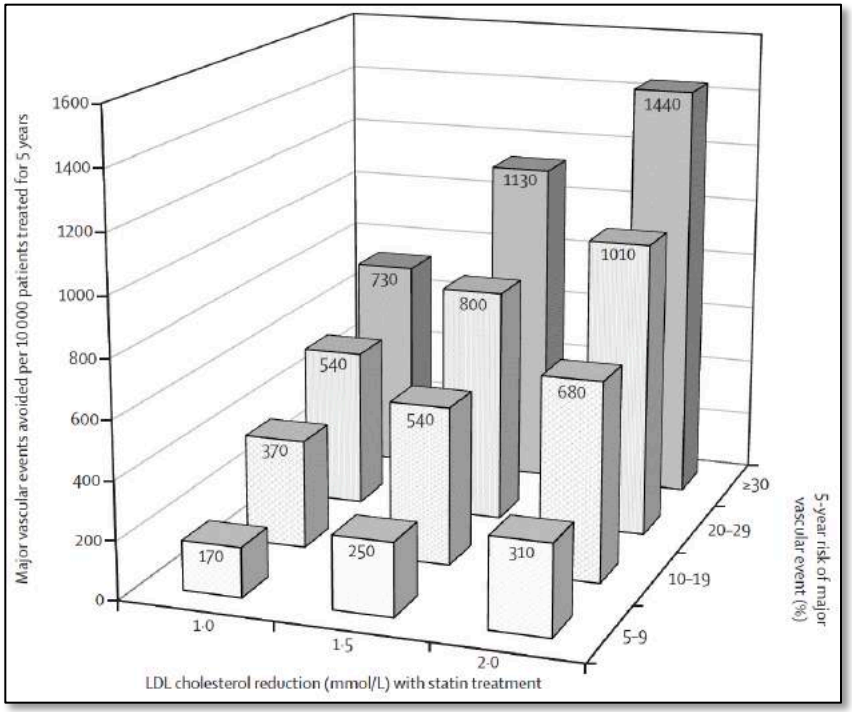
The Lancet September 8th, 2016

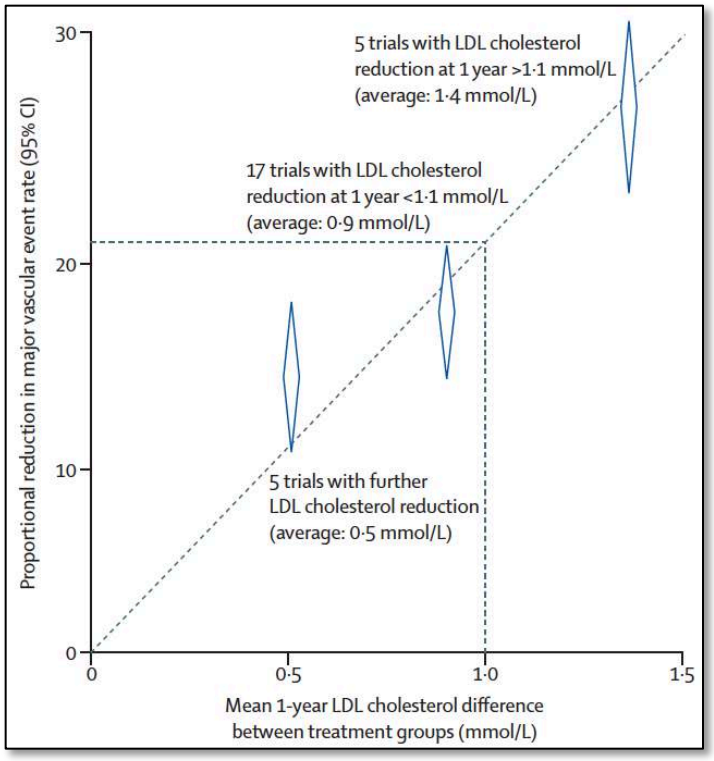
Statines – les évidences



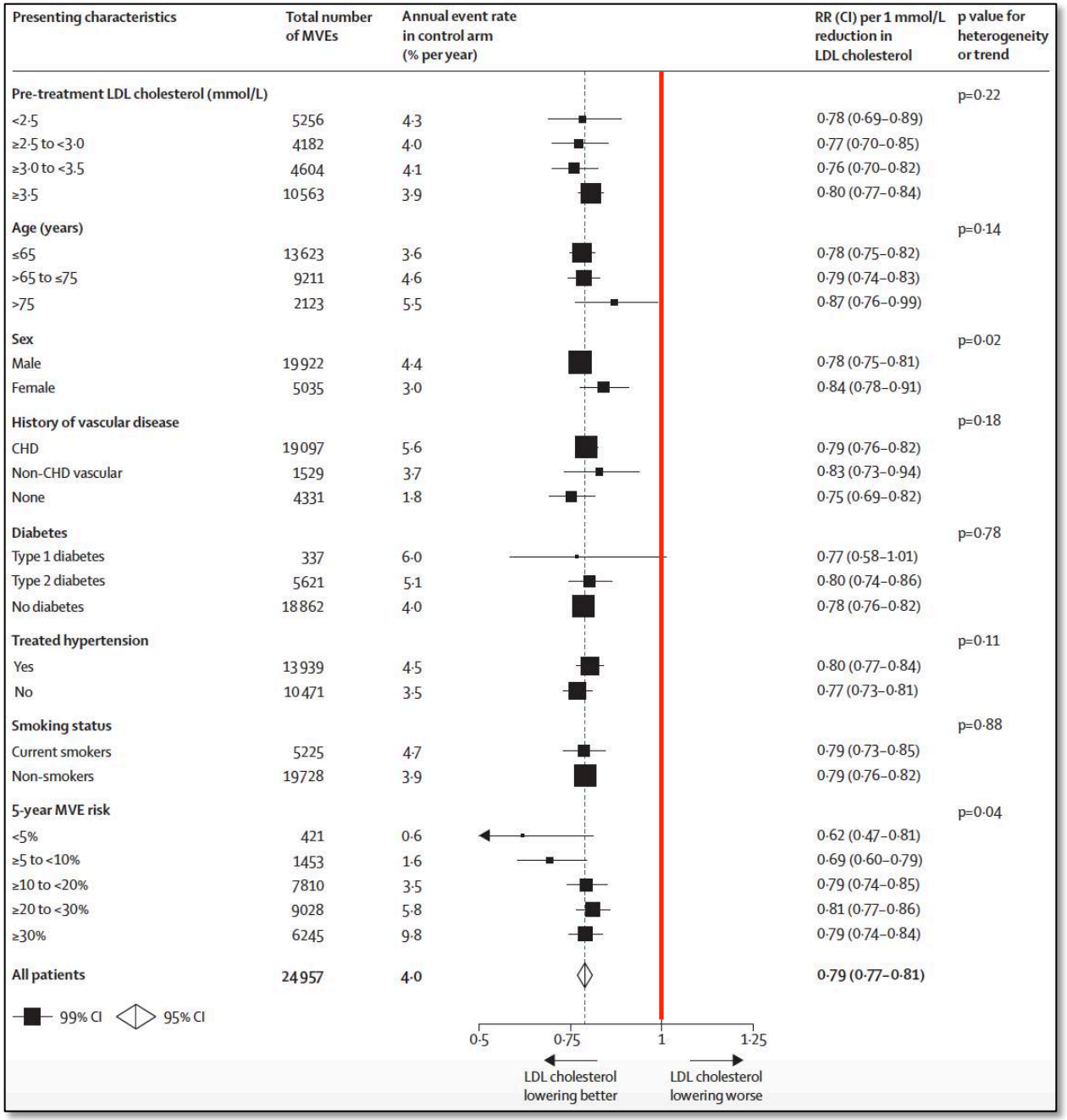
The Lancet September 8th, 2016

Statines – les évidences



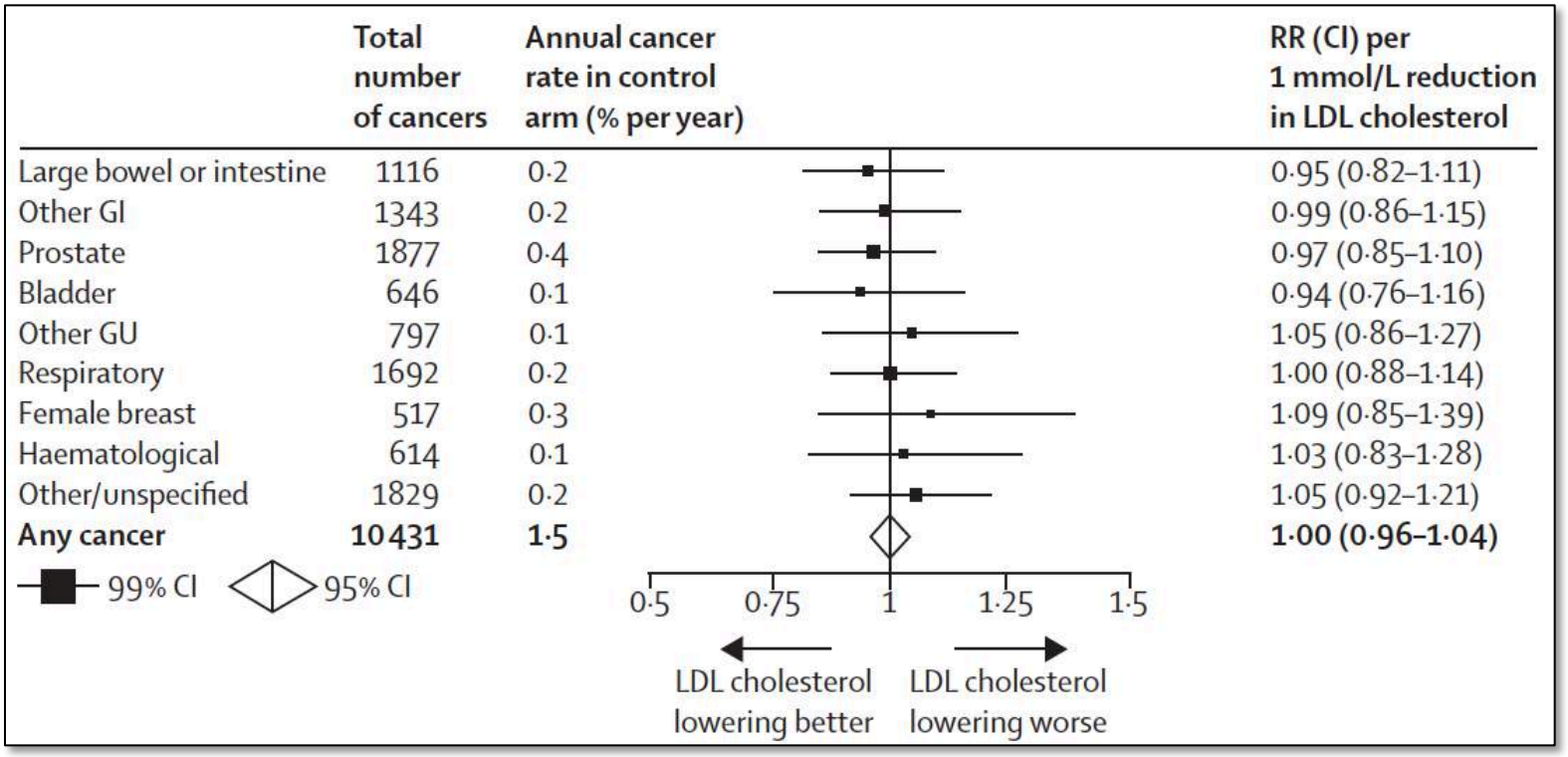


The Lancet September 8th, 2016



The Lancet
Sept 8, 2016
online

Statines – les évidences



The Lancet September 8th, 2016

Statines – les évidences

Myopathy: (about 1 case per 10 000 people treated per year) and even smaller excesses in the incidence of rhabdomyolysis (about 2-3 cases per 100 000 treated per year). It usually resolves rapidly when statin therapy is stopped.

New-onset diabetes: the absolute excess was about 10-20 per 10 000 per year. There is also no good evidence of an excess of microvascular complications related to diabetes with statin therapy (as described below).

Haemorrhagic strokes: an absolute excess of about 5-10 per 10 000 patients in whom LDL cholesterol is reduced by 1-2 mmol/L for 5 years with statin therapy. The increase in haemorrhagic stroke is outweighed by the reduction in the risk of ischaemic stroke.

The Lancet September 8th, 2016

Statines – les évidences

Symptomatic muscle pain: would appear to be no more than about 10-20 cases yearly per 10 000 treated individuals, with only about one of those cases associated with substantial elevations in creatine kinase concentrations (ie, myopathy) and requiring statin therapy to be stopped.

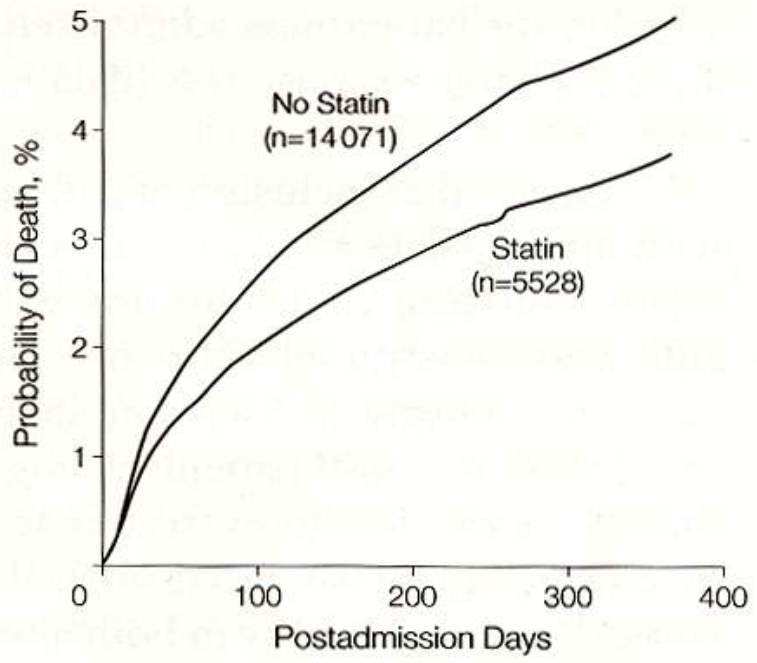
Neuro-cognitive function: given the weight of evidence against adverse effects of statin therapy on memory or other aspects of cognition, it would now be appropriate for regulatory authorities to consider their removal from lists of potential adverse effects on the drug labels so that patients are not inappropriately deterred from using statin therapy.

The Lancet September 8th, 2016

Statines – les évidences

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

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; $P=.001$).

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.

Le traitement de statine après infarctus sauve des vies.

JAMA 2001;285:430

Statines – les évidences

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

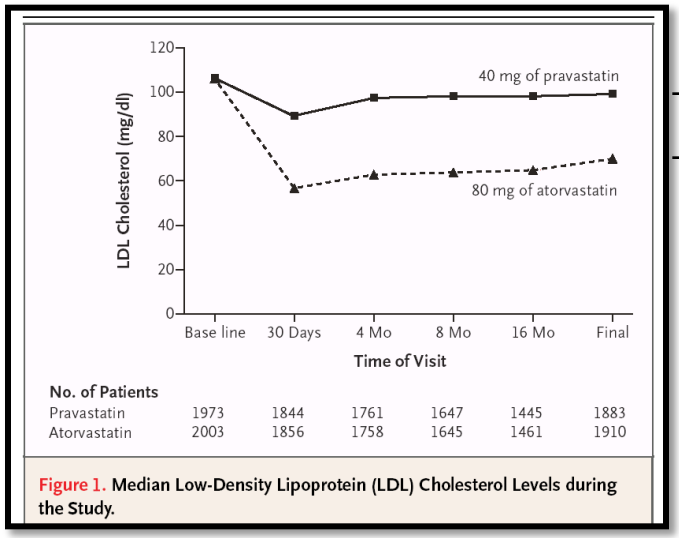
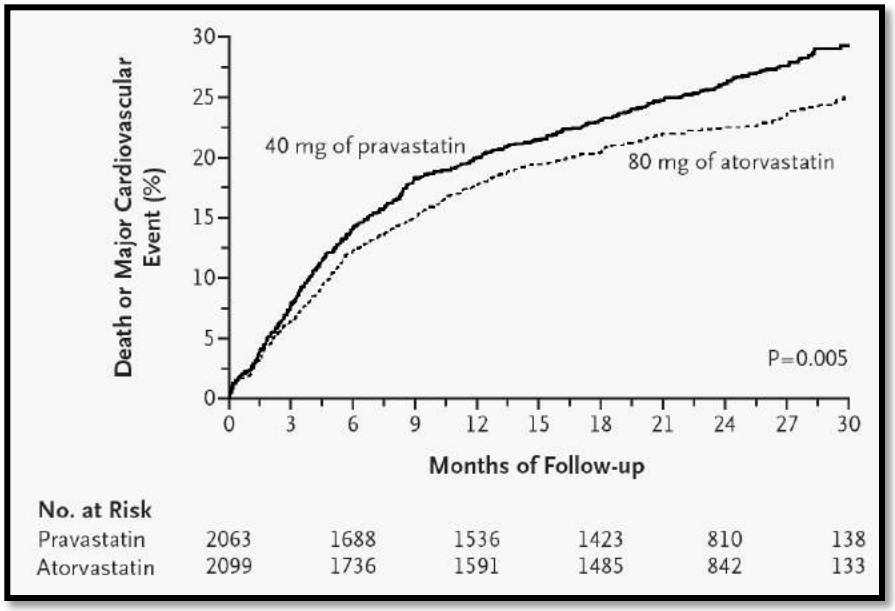


Figure 1. Median Low-Density Lipoprotein (LDL) Cholesterol Levels during the Study.

→ 2.6 mmol/l

→ 1.8 mmol/l



Supported by Bristol-Myers Squibb and Sankyo.

N Engl J Med 2005;352:20

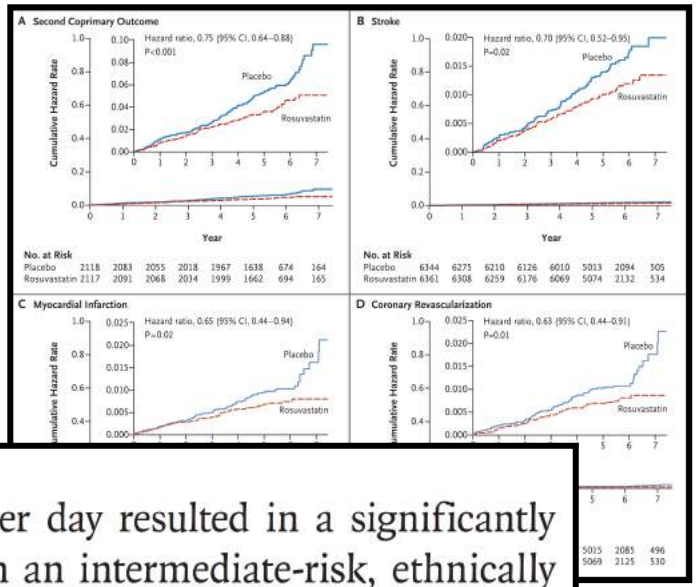
Statines – les évidences

HOPE-3 (statin alone)

ORIGINAL ARTICLE

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

S. Yusuf, J. Bosch, G. Dagenais, J. Zhu, D. Xavier, L. Liu, P. Pais, P. López-Jaramillo, L.A. Leiter, A. Dans, A. Avezum, L.S. Piegas, A. Parkhomenko, K. Keltai, M. Keltai, K. Sliwa, R.J.G. Peters, C. Held, I. Chazova, K. Yusoff, B.S. Lewis, P. Jansky, K. Khunti, W.D. Toff, C.M. Reid, J. Varigos, G. Sanchez-Vallejo, R. McKelvie, J. Pogue,* H. Jung, P. Gao, R. Diaz, and E. Lonn, for the HOPE-3 Investigators†



CONCLUSIONS

Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)

Funding was provided by the Canadian Institutes of Health Research and AstraZeneca. AstraZeneca provided the trial drug, served as a single voting member on the 24-member steering committee, and had no other role in the trial.

NEJM April 2, 2016;374:21

Dyslipidémies - Guidelines

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Dyslipidémies cibles

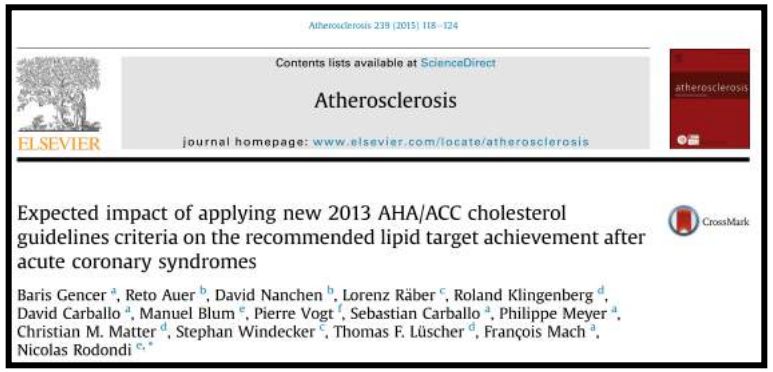
Table 9 Recommendations for lip
treatment targets in the prevention
disease

Recommendations	Class
LDL-C is recommended as the primary target for treatment.	I
TC should be considered as a treatment target if other analyses are not available.	IIa
Non-HDL-C should be considered as a secondary treatment target.	IIa
ApoB should be considered as a secondary treatment target, when available.	IIa
HDL-C is not recommended as a target for treatment.	III
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class [a]	Level [b]	Ref [c]
In patients at VERY HIGH CV risk[e], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[e], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

Malgré les bénéfices des traitements hypolipémiants, de nombreux patients en prévention secondaire n'atteignent pas les valeurs cibles de LDL-c



Atherosclerosis 239 (2015) 118–124

Contents lists available at ScienceDirect

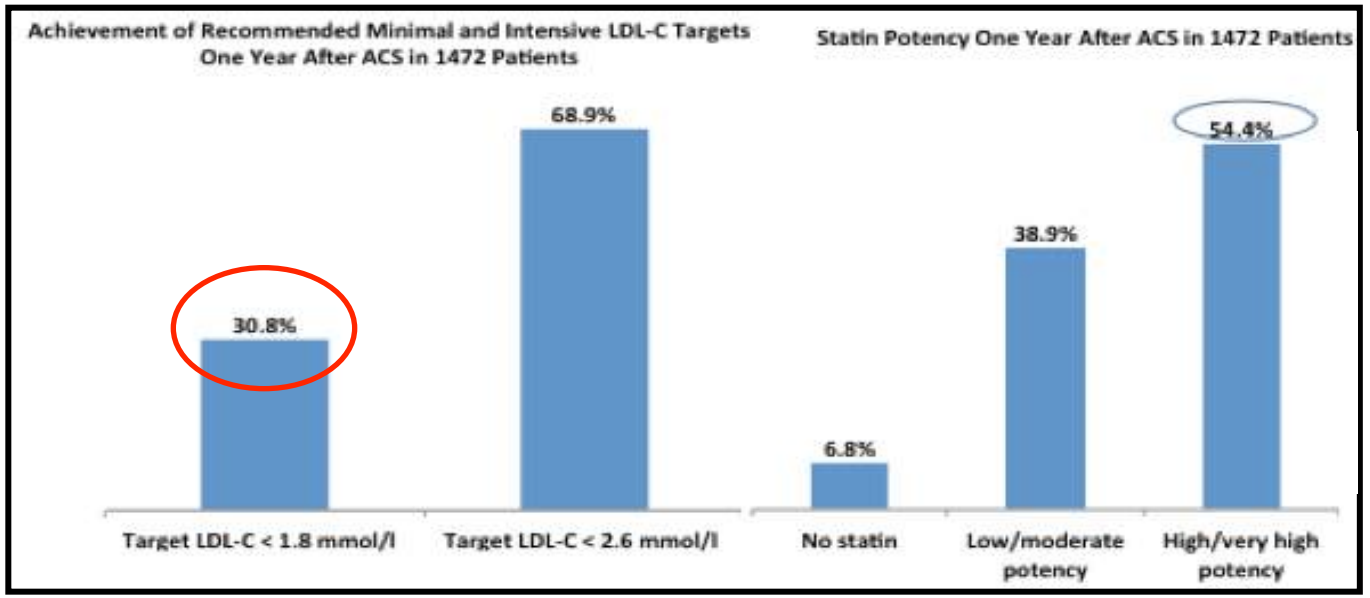
Atherosclerosis

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

Expected impact of applying new 2013 AHA/ACC cholesterol guidelines criteria on the recommended lipid target achievement after acute coronary syndromes

Baris Gencer [a], Reto Auer [b], David Nanchen [b], Lorenz Räber [c], Roland Klingenberg [d], David Carballo [a], Manuel Blum [e], Pierre Vogt [f], Sebastian Carballo [a], Philippe Meyer [a], Christian M. Matter [d], Stephan Windecker [c], Thomas F. Lüscher [d], François Mach [a], Nicolas Rodondi [c,*]

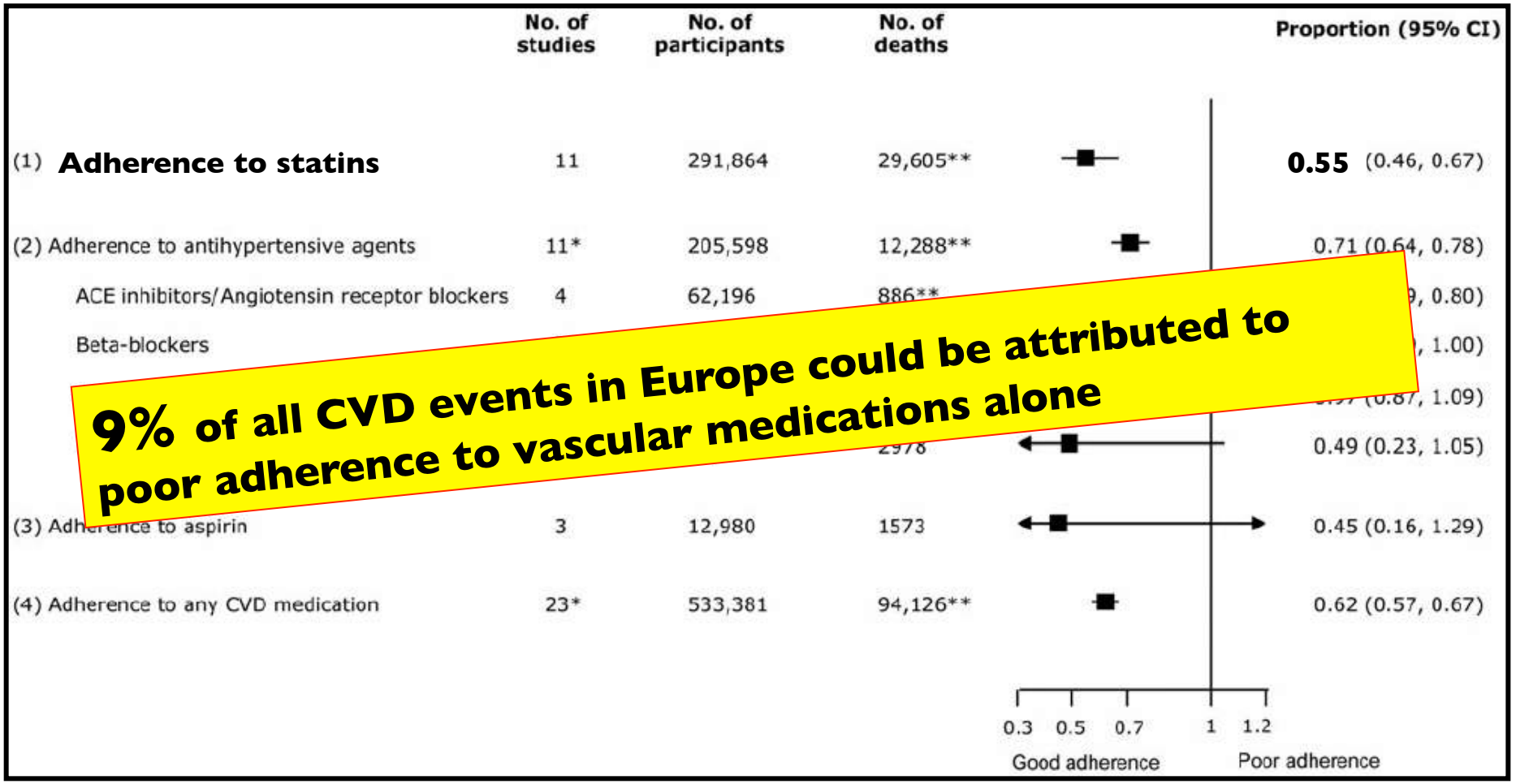
- SPUM-ACS (Bern-Genève-Lausanne-Zurich)
  - n=1472 après syndrome coronarien aigu
  - 30% à la valeur cible de 1.8 mmol/L après 12 mois



Atherosclerosis 2015;239:118-24

Relative risk of death for adherence > 80% versus < 80%

Meta-analysis of 44 studies, n= 1 978 919; 135 627 CVD events; 94 126 cases of all-cause mortality

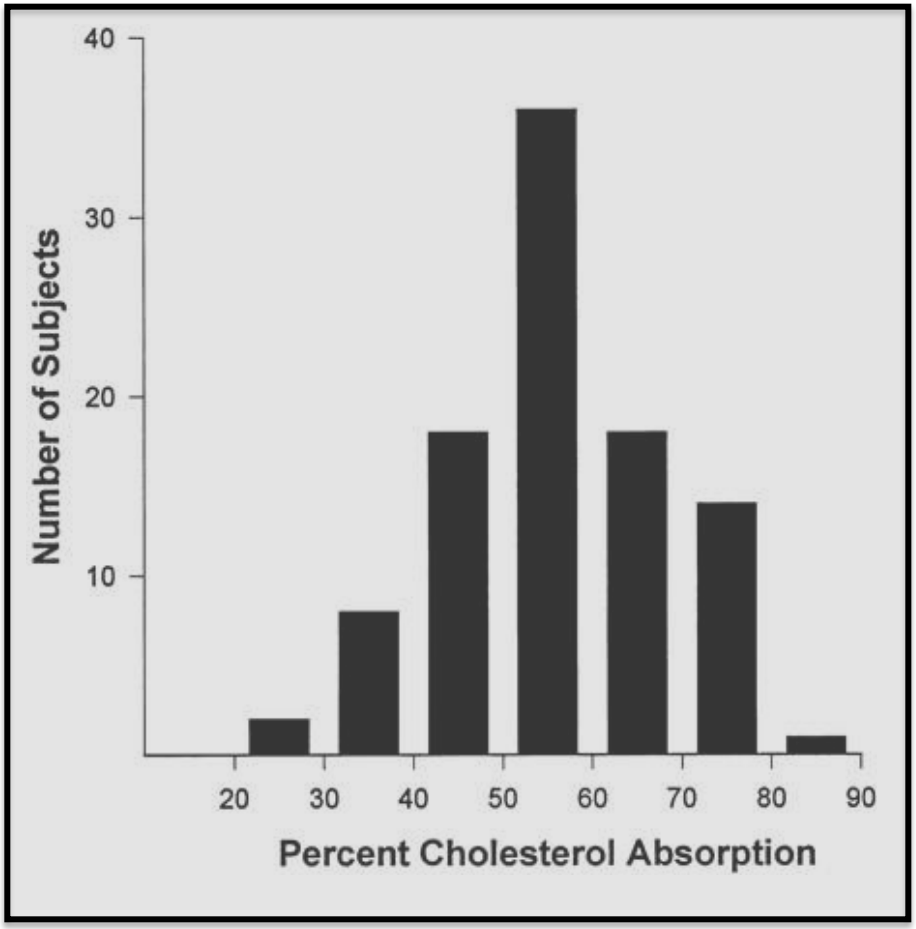


9% of all CVD events in Europe could be attributed to poor adherence to vascular medications alone

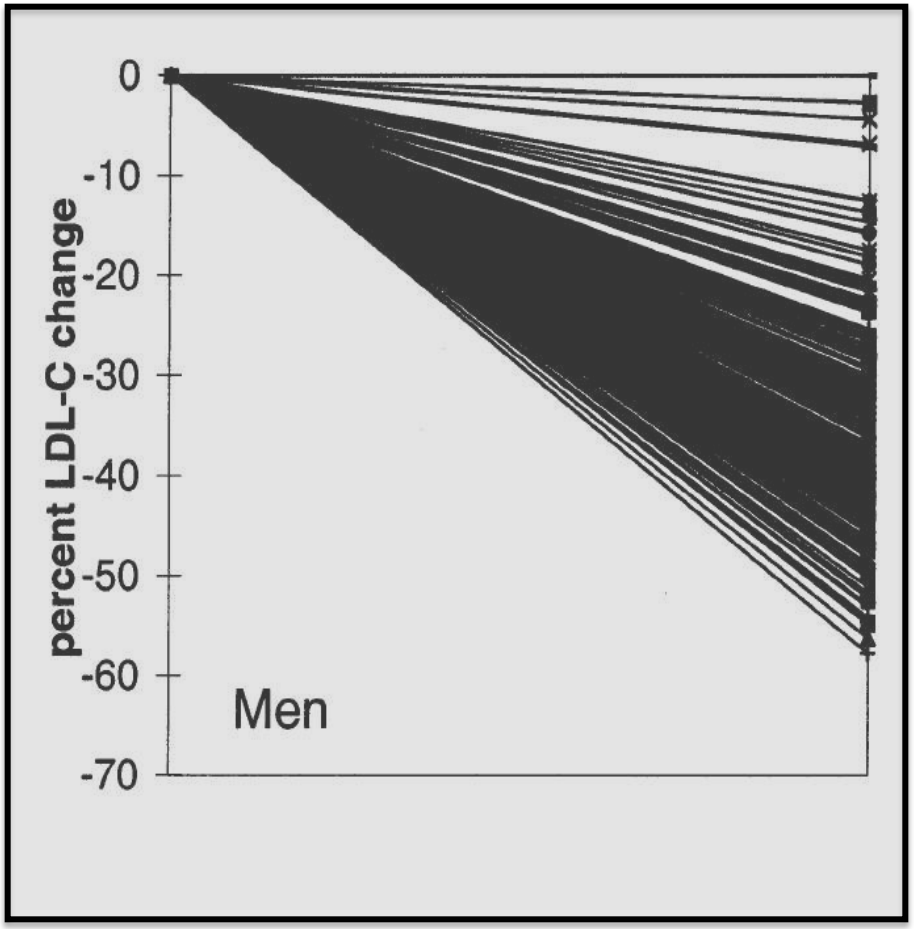
Eur Heart J 2013;34:2940

Great variability in statin response

Response to 10mg Atorvastatin



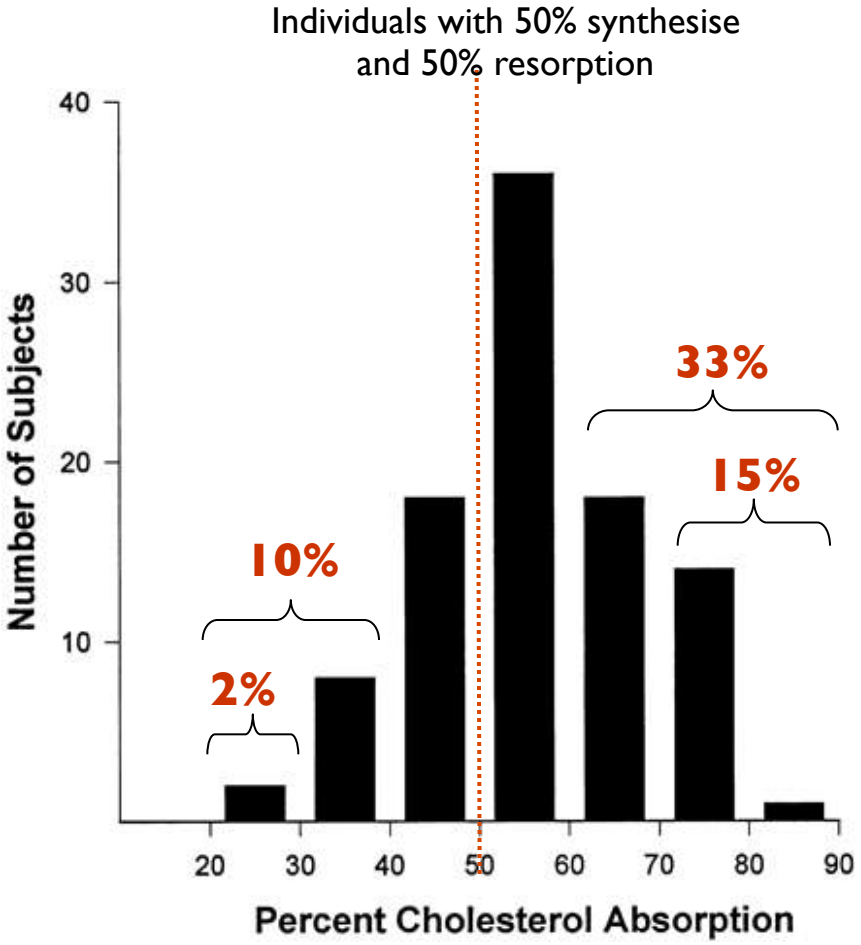
J Lipid Res 1999;40:302



Atherosclerosis 2001;158:183

Broad variation of LDL-C lowering

Cholesterol absorption in the general population:
1-3 of 10 persons are "high absorbers"



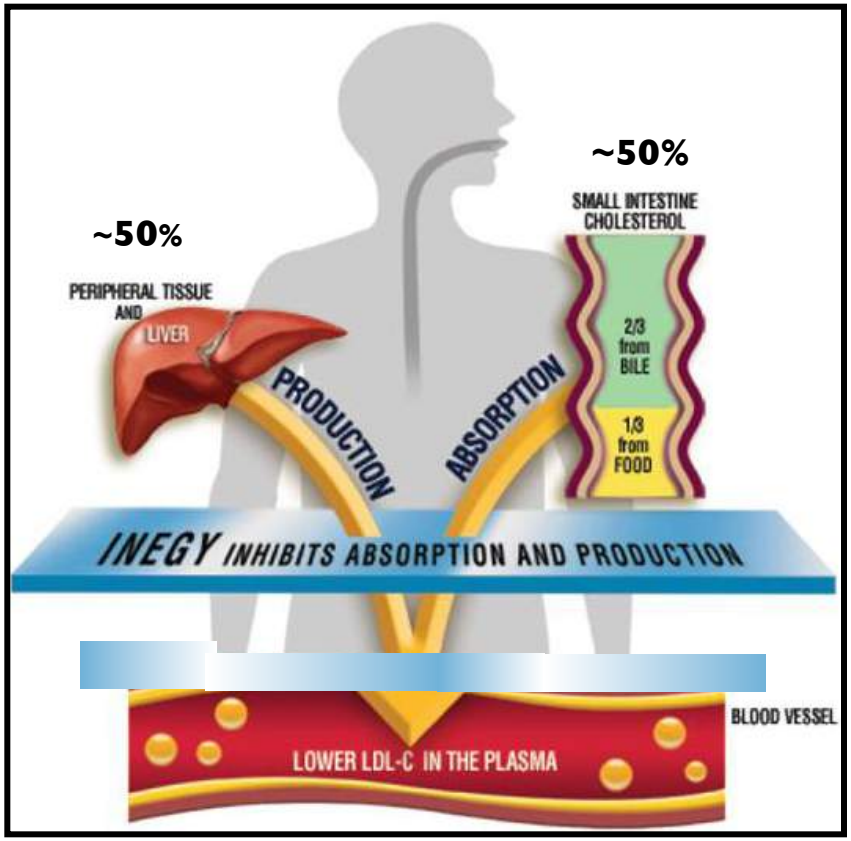
- 15% of the general population are extreme "high absorber" and 2% are extreme "high synthetizer"

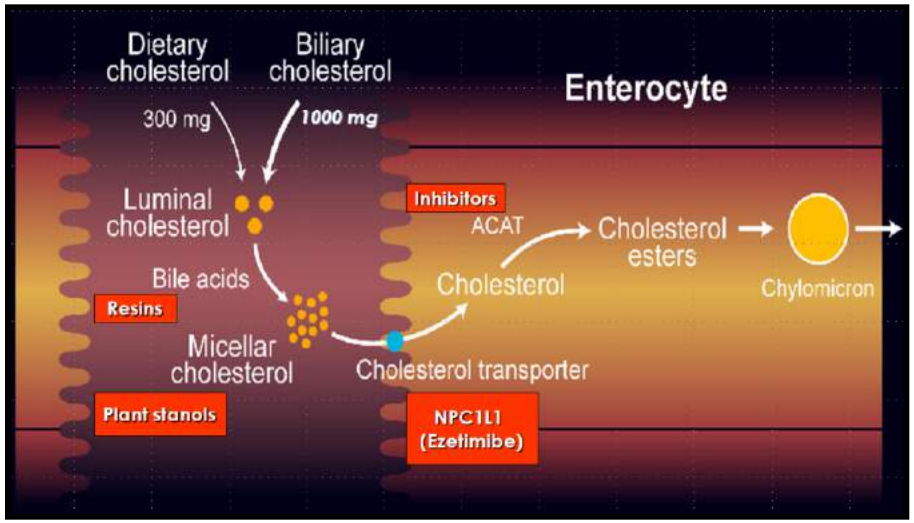
- In about 1/3 of the population the rate of cholesterol absorption is > 60% and in about 10% the rate of cholesterol-synthesis >60%

-> high absorber do not or little respond to statin therapy
-> high synthesizer: the contrary

J Lipid Res 1999;40:302

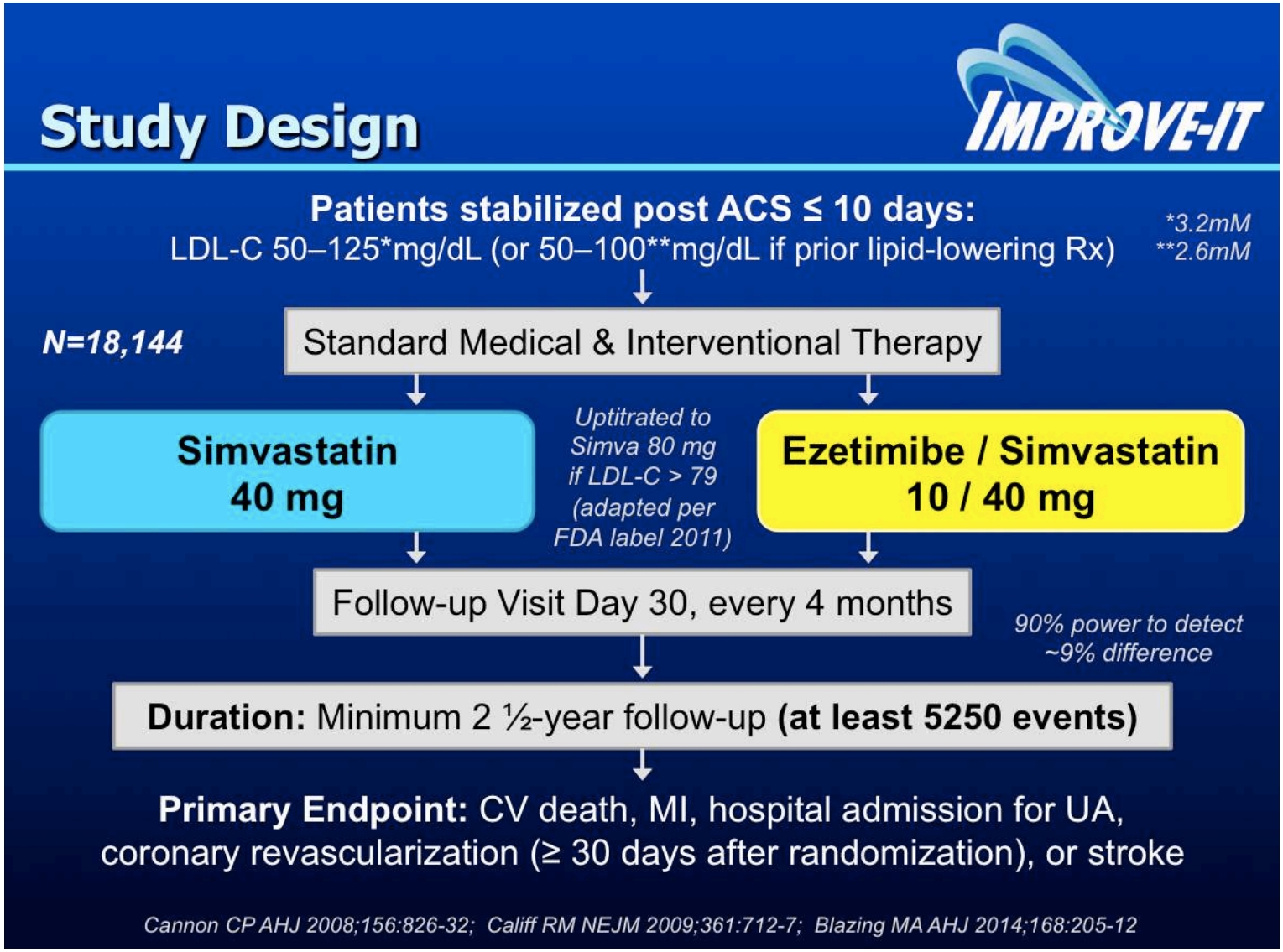
Counter-regulation of cholesterol absorption and synthesis





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

LDL-cholesterol – Is lower better ?



LDL-cholesterol – Is lower better ?

IMPROVE-IT Primary Endpoint - ITT

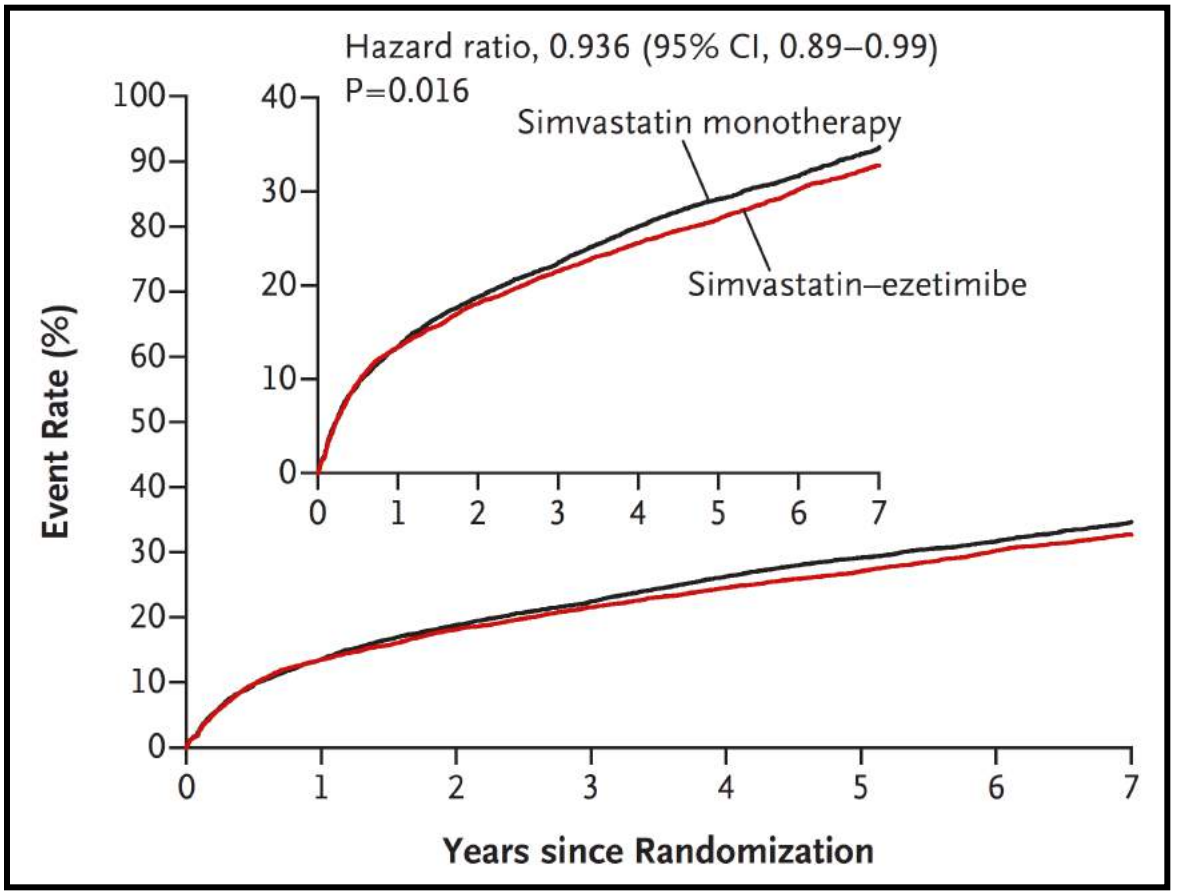
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

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*



NEJM June 3, 2015;372:2387-97

LDL-cholesterol – Is lower better ?

IMPROVE-IT shows benefit:

First study, to show an additional benefit ***by adding*** a ***non-statin-drug*** to the statin therapy.

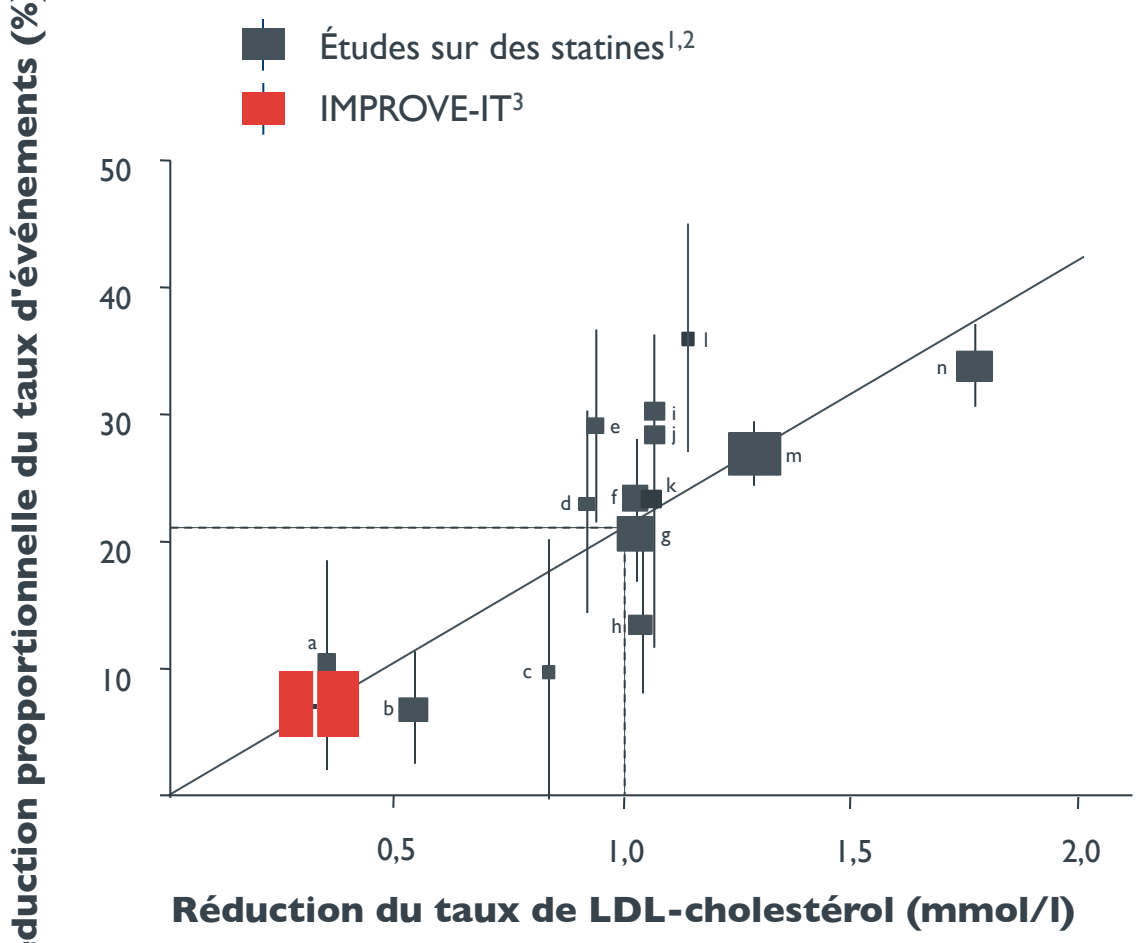
Non statin lowering of LDL-c with Ezetimibe (in addition to a statin) additionally lowers CV events.

Even lower LDL-c is even better !

Lipid-theory: lowering LDL-c reduces CV events, again confirmed

Guidelines should be reviewed.

Méta-analyse CTT: rapport linéaire entre la réduction absolue du taux de LDL-C et la réduction proportionnelle des événements vasculaires



Baisse du taux de LDL-C en mesure de 1 mmol/l (38,7 mg/dl) sur 5 ans:

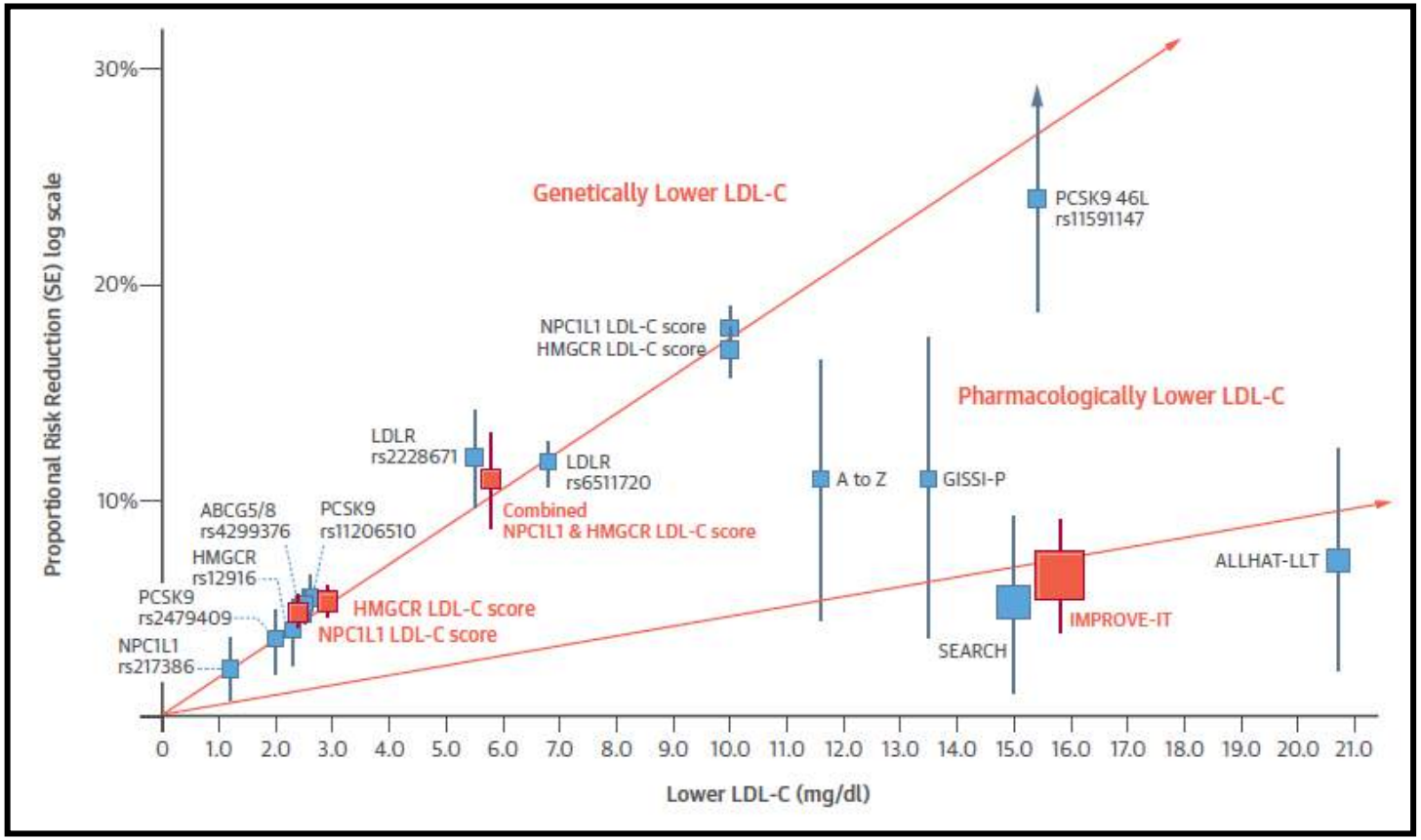
- Réduction de 12% de la mortalité totale
- Réduction de 19% de la mortalité coronarienne
- Réduction de 21% d'évènements tels qu'un infarctus du myocarde ou un AVC

Modifié d'après: Baigent C et al., CTT Collaborators. Lancet, 2005 Oct 8;366(9493):1267-78. CTT Collaboration, Baigent C et al. Lancet, 2010 Nov 13;376(9753):1670-81. Cannon CP et al.; IMPROVE-IT Investigators. N Engl J Med. 2015 Jun 18;372(25):2387-97

La preuve génétique: le LDL-c est un facteur de risque cardiovasculaire

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



JACC 2015;65:1552-61

PCSK9
(Proprotein Convertase Subtilisin/Kexin 9)

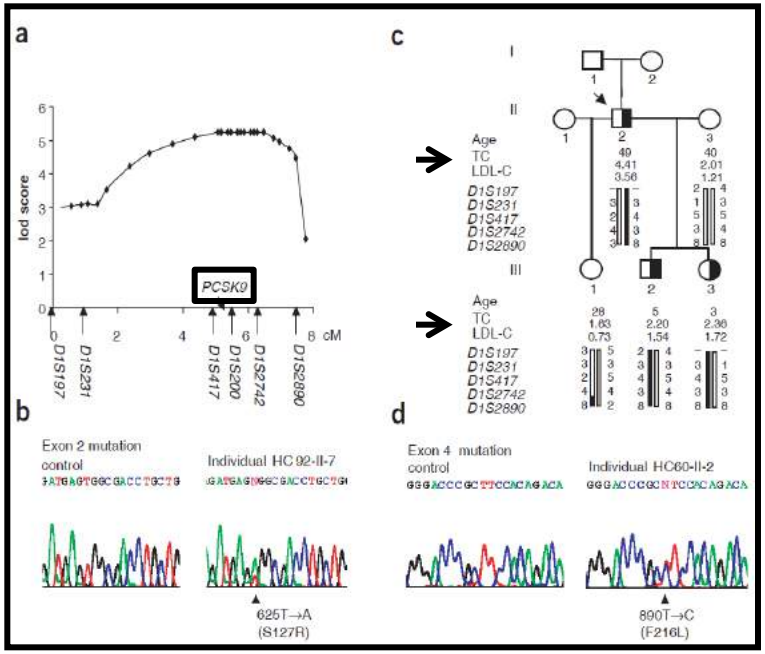
Gain of function mutations in PCSK9 in humans

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



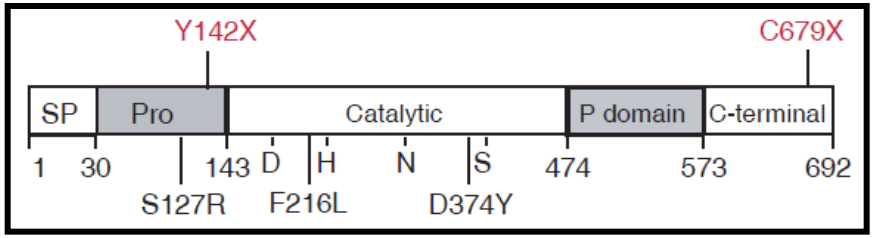
Nature Genetics 2003;34:154

Loss of function mutations in PCSK9 in humans

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% European Americans



Nature Genetics 2005;37:161

Cholesterol metabolism in PCSK9 knock-out mice

PCSK9$^{-/-}$ mice are compared to wild type mice at 12 weeks of age

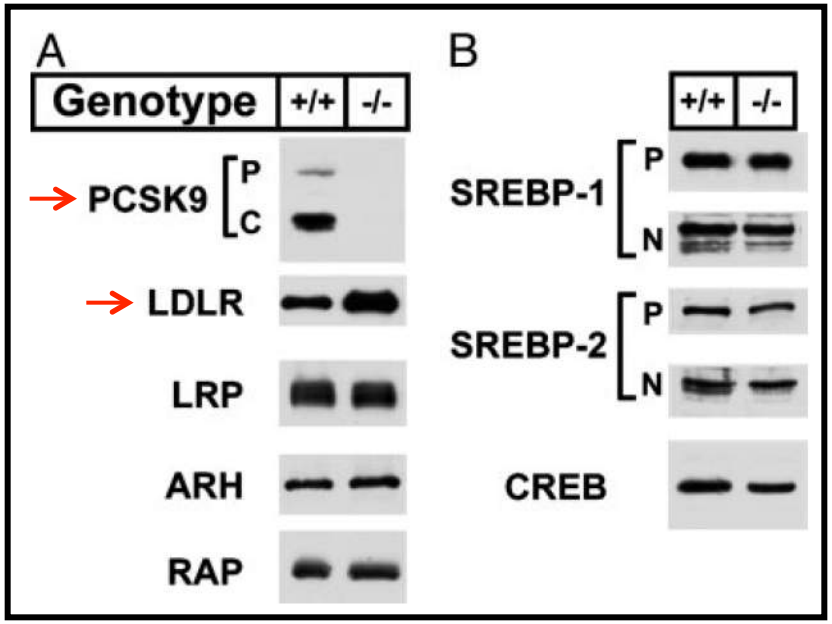
Both groups were fed normal rodent chow ad libitum

Body weight may be slightly higher in PCSK9$^{-/-}$ 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

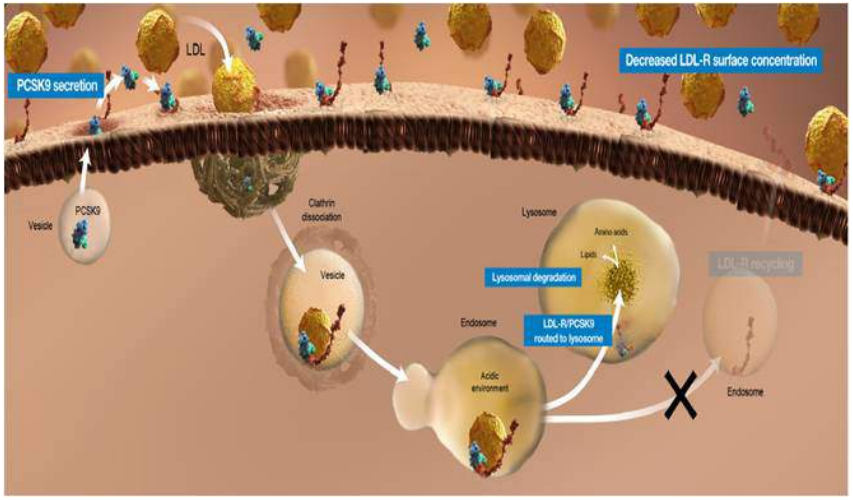
Parameter	WT	*Pcsk9*$^{-/-}$
No. of mice	4	4
Body weight, g	25.5 ± 0.6	30.0 ± 1.6
Liver cholesterol, mg/g	2.20 ± 0.16	2.00 ± 0.02
Liver TG, mg/g	9.2 ± 0.6	7.2 ± 0.7
Plasma cholesterol, mg/dl	95.7 ± 9.4	→ 46.3 ± 1.9*
Plasma TG, mg/dl	70.0 ± 11	85.8 ± 7.5



PNAS 2005;102:5374

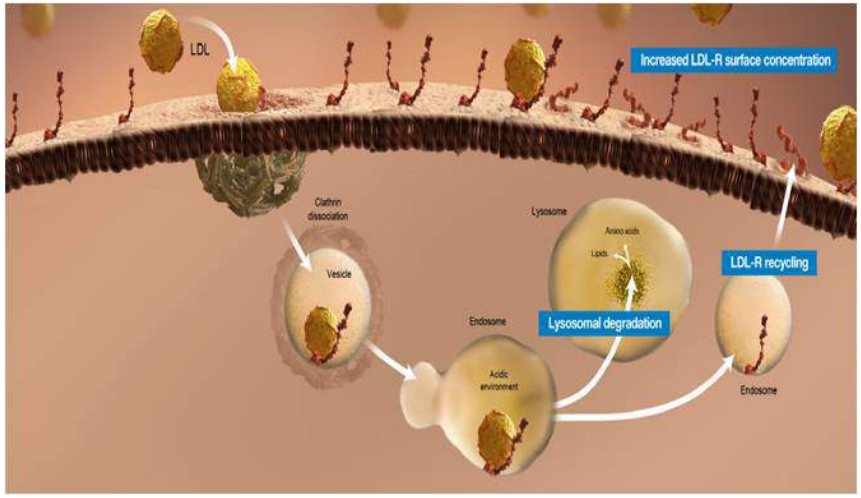
PCSK9 is a regulator of hepatic LDL receptor expression

Presence of PCSK9



- Less LDL-R
- Higher plasma LDL-C

Absence of PCSK9



- More LDL-R
- Lower plasma LDL-C

Qian YW, Schmidt RJ, Zhang Y, et al. J Lipid Res. 2007;48:1488-1498
Horton JD, Cohen JC, Hobbs HH. J Lipid Res. 2009;50(suppl):S172-S177
Rashid S et al. PNAS USA 2005;102:*5374-5379*
Brown MS, Goldstein JL. PNAS USA1979;76:3330-3337
Steinberg D, Witztum JL. PNAS USA 2009;106:9546-9547
Goldstein JL, Brown MS. ATVB 2009;29:431-438

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

Am J Hum Genetics 2006;79:514-23
32 yo woman
Compound heterozygote for 2 LOF alleles in PCSK9
LDL-c 0.36 mmol/L
Fertile, college educated, physically coordinated
(fitness instructor)

Atherosclerosis 2007;193:445-8
African woman
Homozygote C679X
LDL-c 0.40 mmol/L
Healthy with children

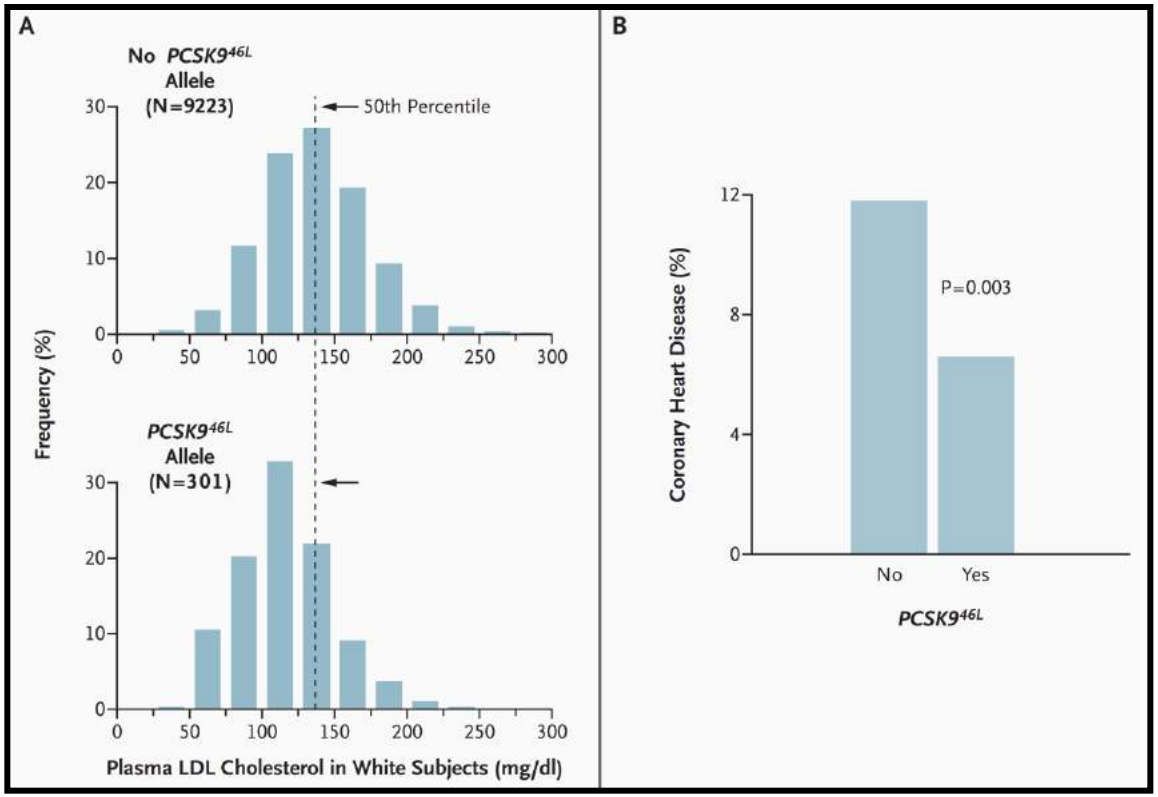
Loss of function mutations for PCSK9 in humans are associated with CHD risk reduction

The NEW ENGLAND JOURNAL of MEDICINE

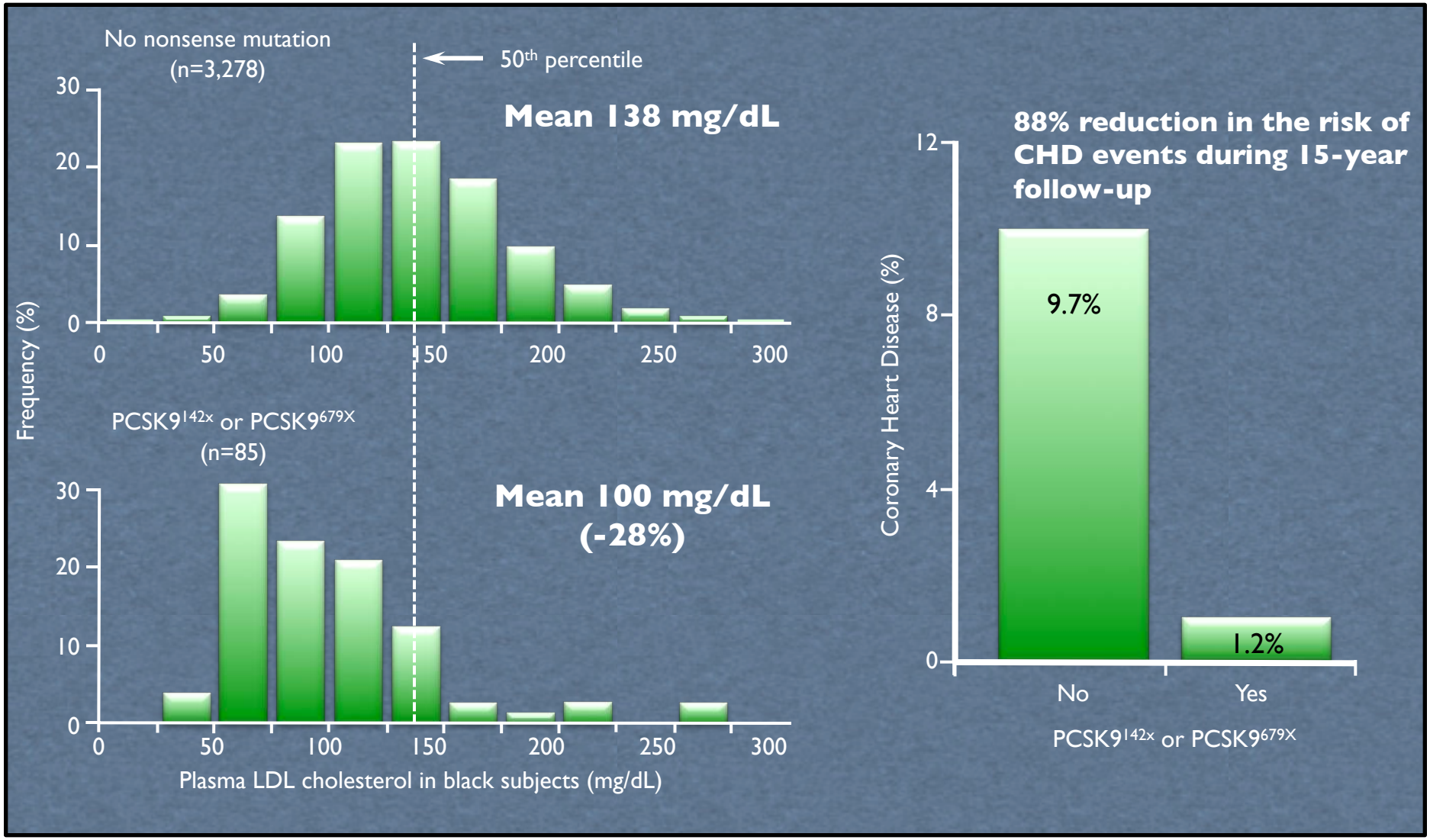
ORIGINAL ARTICLE

Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

NEJM 2006;354:1264

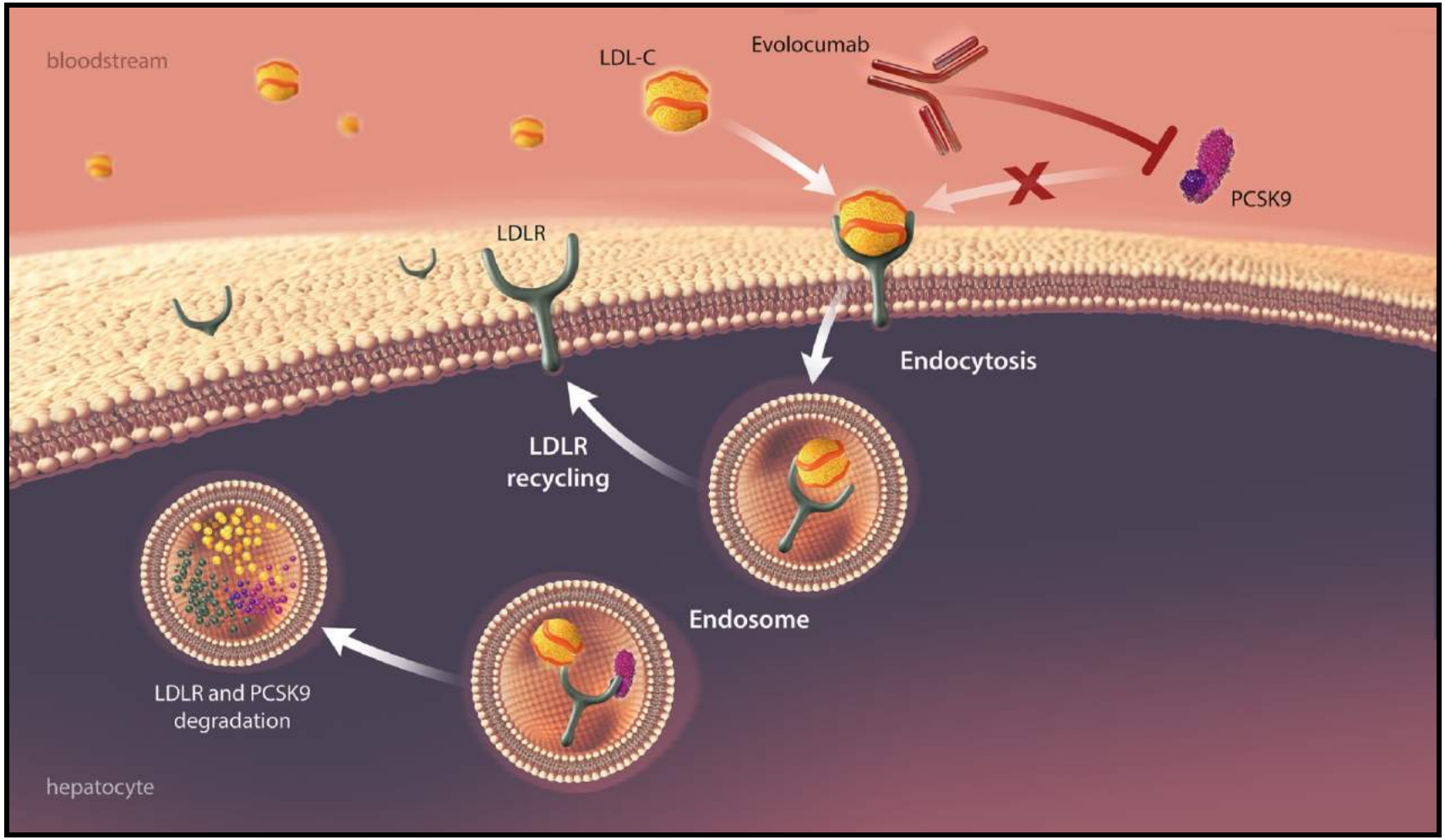


Loss of function mutations for PCSK9 in humans are associated with CHD risk reduction



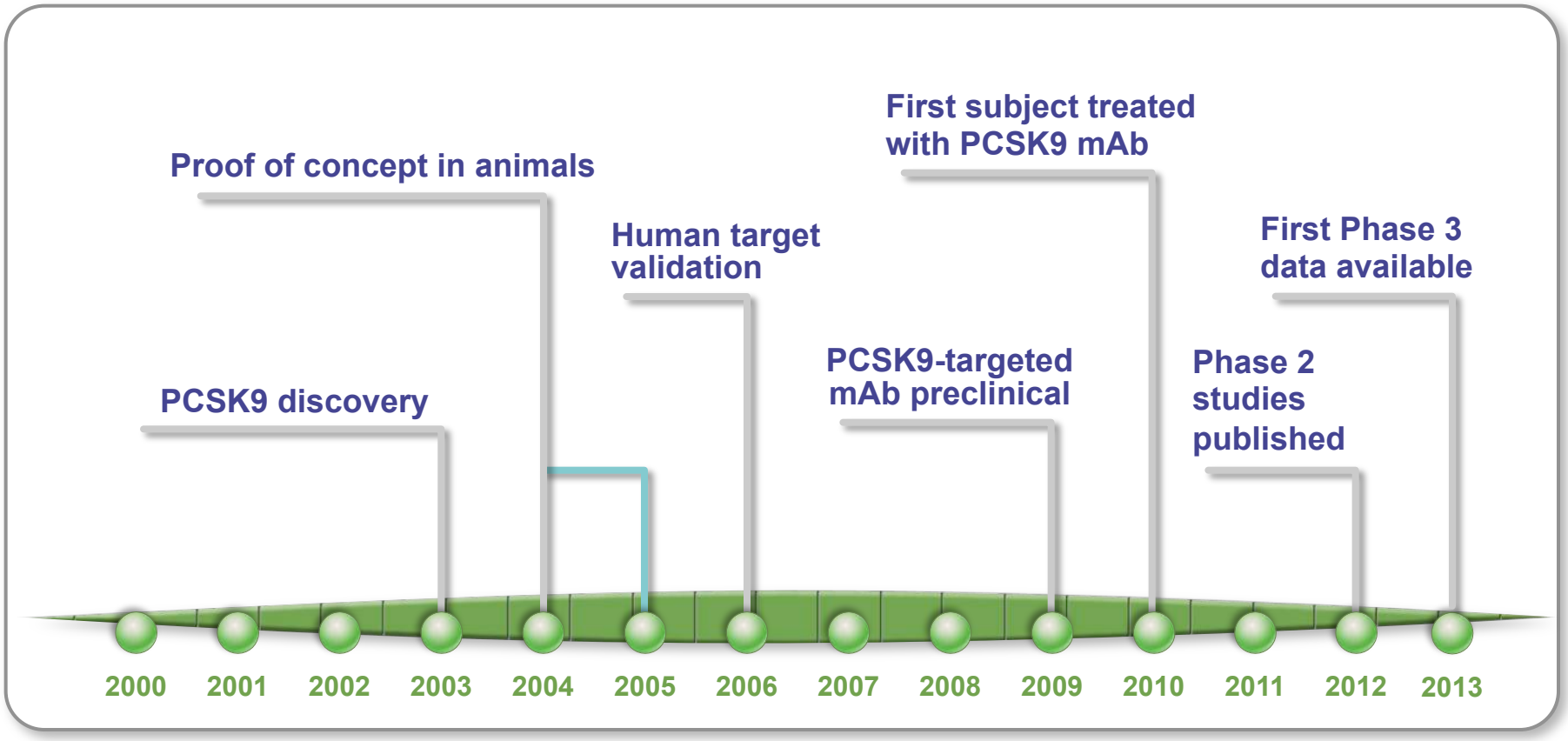
Adapted from Cohen JC *et al. NEJM* 2006;354:1264

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



PNAS USA 2009;106:9820-25

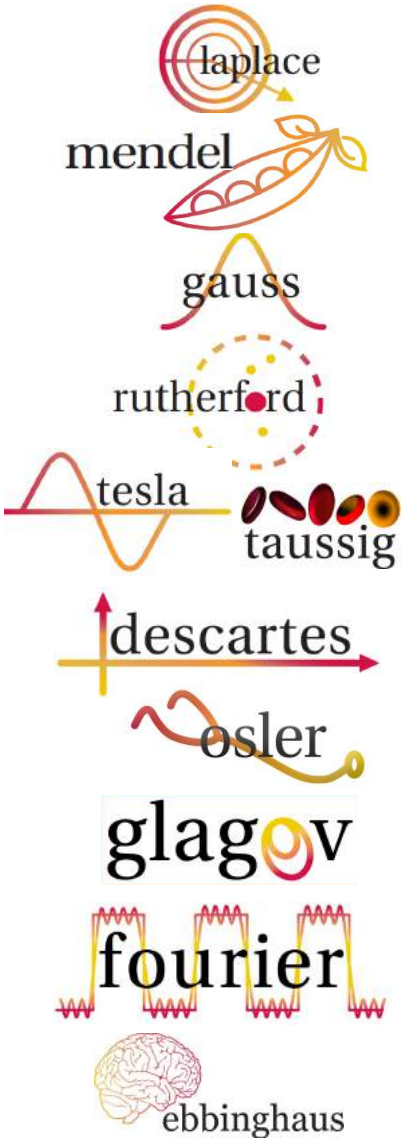
PCSK9 – Rapid progress from bench to clinic in less than a decade



Evolocumab: PROFICIO addresses key areas of unmet need in the management of dyslipidemia

PROFICIO

>35,000 patients



Combination therapy	Phase 2 (n=631)	Published Robinson, JAMA
Monotherapy	Phase 2 (n=411)	Published Koren, JACC
Statin intolerant	Phase 2 (n=160)	Phase (n=30 Published Stroes, JACC
HeFH	Phase 2 (n=168)	Published Raal, Lancet
HoFH/ Severe FH	Phase 2/3 (n=58)	Published Raal, Lancet
Long-term safety and efficacy		Published Blom, NEJM
Open-label extension	Phase 2 (n=1324)	Published Sabatine, NEJM
Atherosclerosis		Phase 3 (n=950)
Secondary Prevention		Phase 3 (n=27,564)
Neurocognition		Phase 3 (n=1972)

HeFH, heterozygous hypercholesterolemia; HoFH, homozygous hypercholesterolemia. ClinicalTrials.gov. Accessed September 2015.

Overview of ODYSSEY Phase 3 clinical trial program

14 global phase 3 trials
Including more than 23'500 patients across more than 2'000 study centers

HeFH population

Add-on to max tolerated statin (± other LMT)

ODYSSEY FH I (EFC12492) N=471
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
18 months

ODYSSEY FH II (CL1112) N=250
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
18 months

ODYSSEY HIGH FH (EFC12732) N=105
LDL-C ≥ 160 mg/dL
18 months

ODYSSEY OLE (LTS13463) N=>1'000
Open label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717
30 months

ODYSSEY LONG TERM (LTS11717) N=2'100
LDL-C ≥ 70 mg/dL
18 months

HC in high CV risk population

Add-on to max tolerated statin (± other LMT)

ODYSSEY COMBO I (EFC11568) N=306
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
12 months

***ODYSSEY COMBO II (EFC11569)** N=660
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
24 months

ODYSSEY CHOICE I (CL1308) N=700
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
12 months

ODYSSEY OUTCOMES (EFC11570)
N=18'000
LDL-C ≥ 70 mg/dL

Additional populations

ODYSSEY MONO (EFC11716) N=100
Patients on no background LMTs
LDL-C ≥ 100 mg/dL
6 months

ODYSSEY ALTERNATIVE (CL1119) N=250
Patients with defined statin intolerance
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

ODYSSEY CHOICE II (EFC13786) N=200
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

ODYSSEY OPTIONS I (CL1110) N=350
Patients not at goal on moderate dose atorvastatin
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

ODYSSEY OPTIONS II (CL1118) N=300
Patients not at goal on moderate dose rosuvastatin
LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
6 months

EAS 2014 | ESC 2014 | AHA 2014 | ACC 2015

ODYSSEY

HC = hypercholesterolemia; LMT = lipid-modifying therapy
*For the ODYSSEY COMBO II other LMT not allowed at entry

Phase 3 Trials: Evolocumab, Alirocumab, Bococizumab

Patient Pop'n	Evolocumab (PROFICIO program)					Alirocumab (ODYSSEY program)					Bococizumab (SPIRE program)				
	Trial	N	Dur'n (m)	Predicted Pt Exposure (Y)	Min B/L LDL-C (mg/dL)	Trial	N	Dur'n (m)	Predicted Pt Exposure (Y)	Min B/L LDL-C (mg/dL)	Trial	N	Dur'n (m)	Predicted Pt Exposure (Y)	Min B/L LDL-C (mg/dL)
HeFH	RUTHERFORD-2	327	3	51	≥100	FH I	471	18	471	≥70	FH	300	12	200	>70
						FH II	250	18	250	≥70					
	HAUSER (paeds)	150	6	50	≥130	HIGH FH	105	18	105	≥160					
HoFH	TESLA	50	3	8	≥130										
	TAUSSIG (OL)	300	60	1000	≥100										
Combo Therapy	LAPLACE-2	1896	3	258	≥80	COMBO I	316	12	209	≥ 70	HR	600	12	400	>70
						COMBO II	720	24	958	≥70					
						OPTIONS I	345	6	51	≥70	LDL	1932	12	1288	>70
						OPTIONS II	300	6	150	≥70					
Monotherapy	MENDEL-2	614	3	71	≥100	MONO	103	6	24	≥70	AI	300	3	50	≥70
Statin Intolerance	GAUSS-2	307	3	47	None	ALTERNATIVE	314	6	47	≥70	SI	150	6	23	≥70
	GAUSS-3	511	36	984	None										
Long term	DESCARTES	901	12	600	≥75	LONG-TERM	2341	18	2341	≥70	LL	690	12	460	≥100
	OSLER-2 (OL)	3671	24	5904	None	OLE (OL)	1200	28	2800	None					
Atheroma	GLAGOV	970	18	970	≥60										
Totals	Patients 10462		Predicted Pt Yrs ~ 9943			Patients 5465		Predicted Pt Yrs ~ 7302			Patients 3972		Predicted Pt Yrs ~ 2421		
CVD Outcomes	FOURIER	27,564	Event driven	NA	≥70	OUTCOMES	18,000	Event driven	NA	≥70	SPIRE-1	17,000	Event driven	NA	≥70 & <100
											SPIRE-2	9,000	Event driven	NA	≥100
Neurocognitive events	EBBINGHAUS	1972 in FOURIER	End of FOURIER	N/A	≥70										

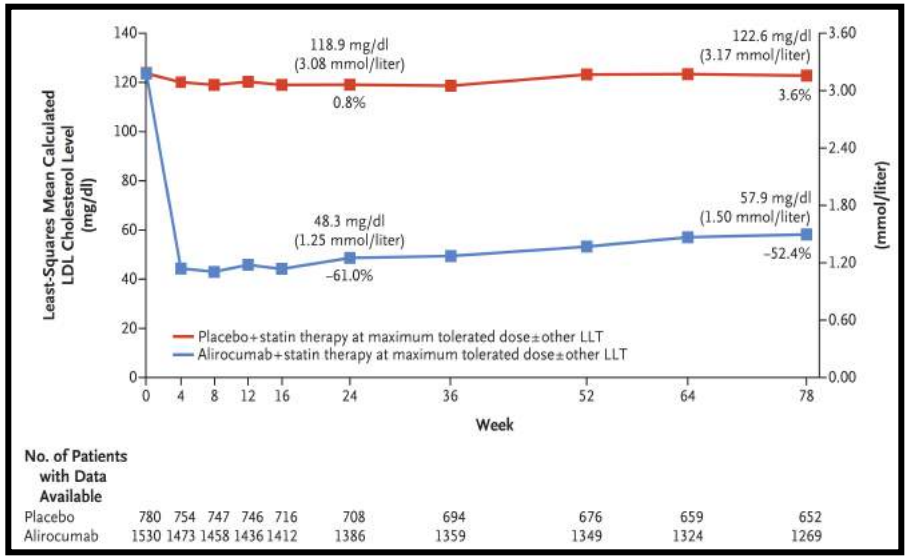
mAb-anti-PCSK9 and LDL-c

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pordy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*



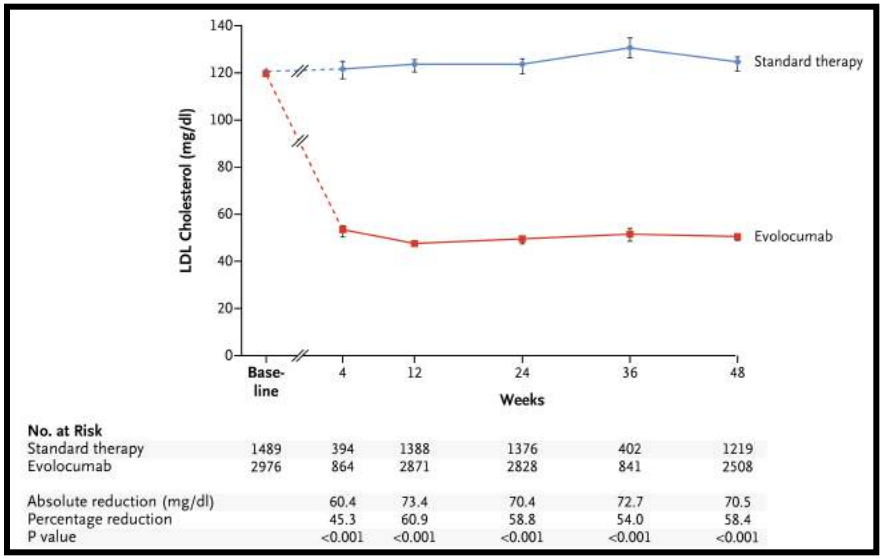
NEJM 2015;372:1489-99

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

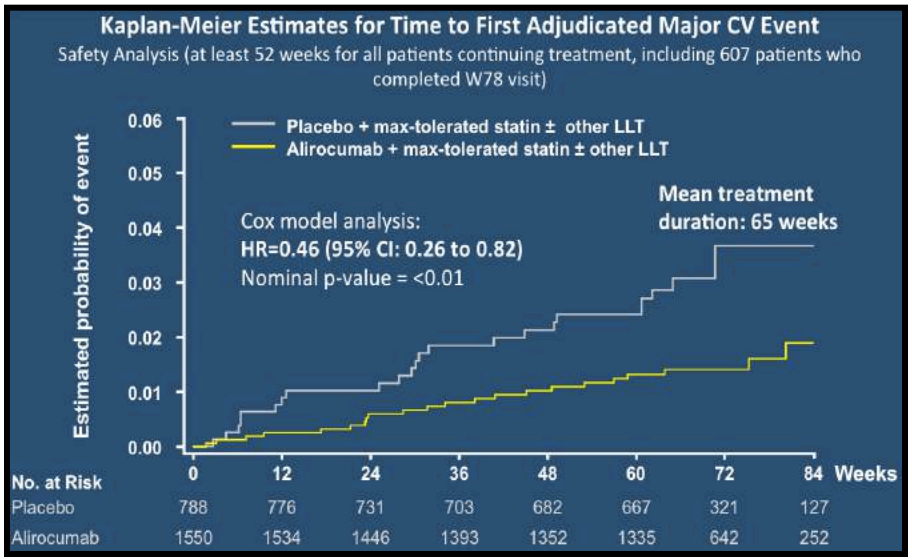
Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

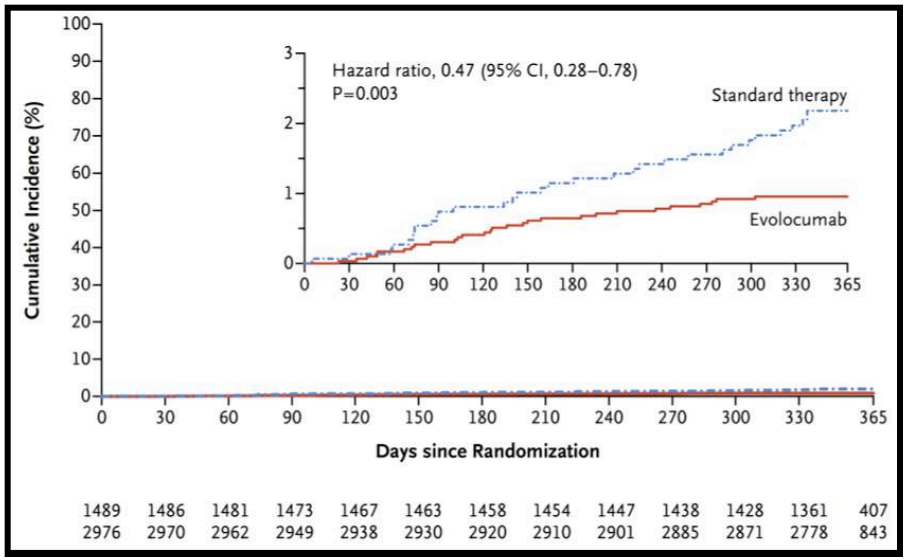


NEJM 2015;372:1500-9

mAB-anti-PCSK9 and CV events

Primary endpoints: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke,UA requiring hospitalisation





ESC Late Clinical Breaking Trial 2014

NEJM 2015;372:1500-9

mAb-anti-PCSK9 and LDL-c

ESC 2016; Hot line Prevention and Lipids / August 29, 2016

ODYSSEY ESCAPE: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients With Heterozygous Familial Hypercholesterolemia Undergoing Lipid Apheresis Therapy

Purpose: A comparison of alirocumab to placebo and the number of LDL aphresis treatments in patients with heterozygous familial hypercholesterolemia.

Trial Design: Phase 3; Randomized, double-blinded, placebo-controlled, parallel group, multi-center (US and Germany). 18-week f/u. N=62. Regular lipid lowering medications + alirocumab 150 mg vs placebo every 2 weeks. Apheresis: fixed-rate of apheresis weeks 1-6; apheresis individualized, weeks 7-18; decrease of LDL-C of 30%, no apheresis.

Primary Endpoint: rate of apheresis treatments over 18 weeks.

Trial Results	alirocumab vs placebo
% reduction in apheresis	75%, $p<0.0001$
No apheresis	63.4% / 0%
Apheresis reduced by half	92.7% / 14.33%

Conclusions: the number of apheresis treatments needed compared to placebo were reduced in those patients treated with the PCSK9 inhibitor alirocumab.

Effects of PCSK9 mAb in adults with hypercholesterolemia

Annals of Internal Medicine REVIEW

Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia

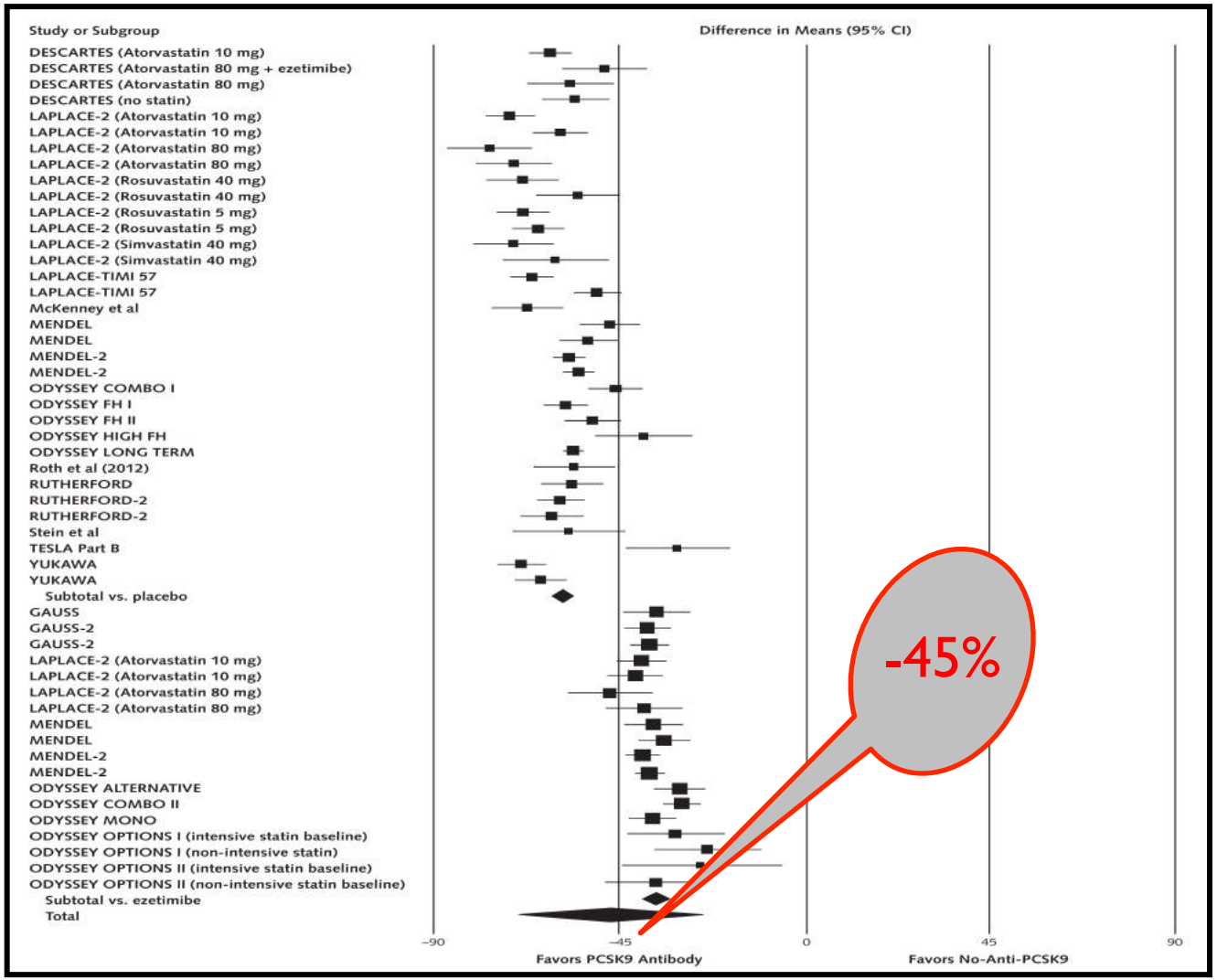
A Systematic Review and Meta-analysis

Eliano Pio Navarese, MD, PhD; Michalina Kołodziejczak, MD; Volker Schulze, MD; Paul A. Gurbel, MD; Udaya Tantry, PhD; Yingfeng Lin, MD; Maximilian Brockmeyer, MD; David E. Kandzari, MD; Julia M. Kubica, MD; Ralph B. D'Agostino Sr., PhD; Jacek Kubica, MD, PhD; Massimo Volpe, MD; Stefan Agewall, MD; Dean J. Kereiakes, MD; and Malte Kelm, MD

Ann Intern Med Jul 7, 2015;163:40-51

Effects of PCSK9 mAb in adults with hypercholesterolemia

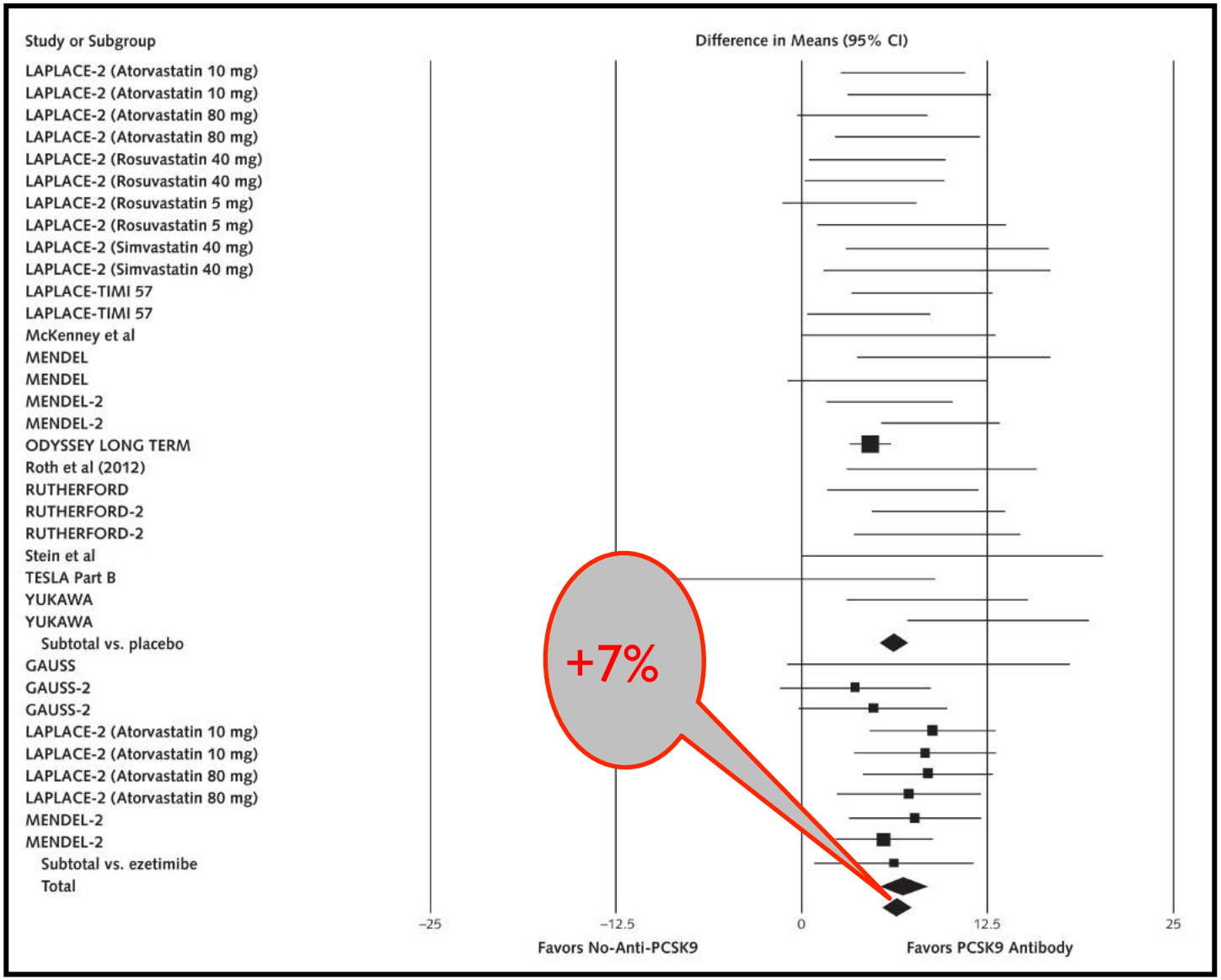
LDL-c percentage of change from baseline



Ann Intern Med Jul 7, 2015;163:40-51

Effects of PCSK9 mAb in adults with hypercholesterolemia

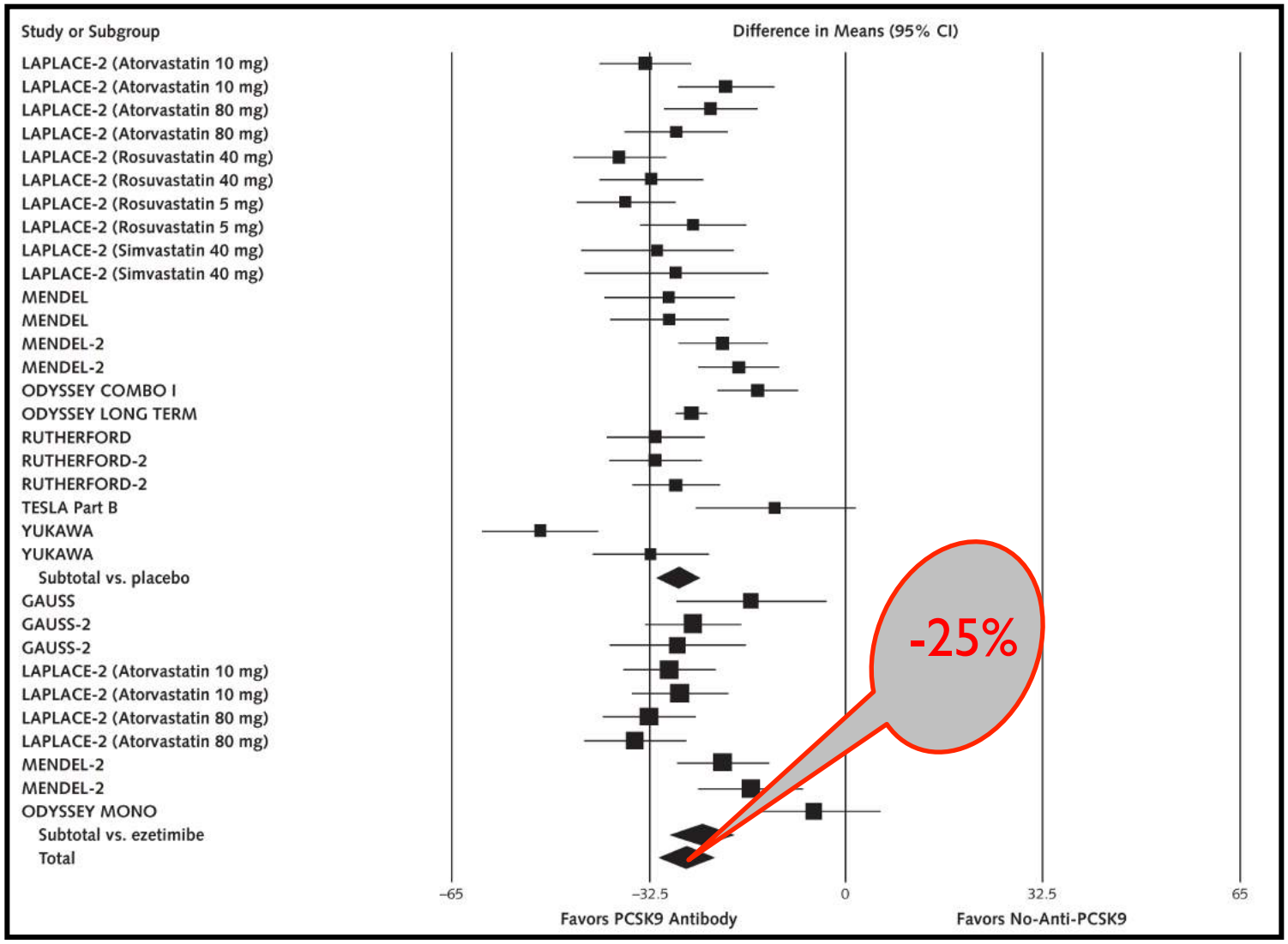
HDL-c percentage of change from baseline



Ann Intern Med Jul 7, 2015;163:40-51

Effects of PCSK9 mAb in adults with hypercholesterolemia

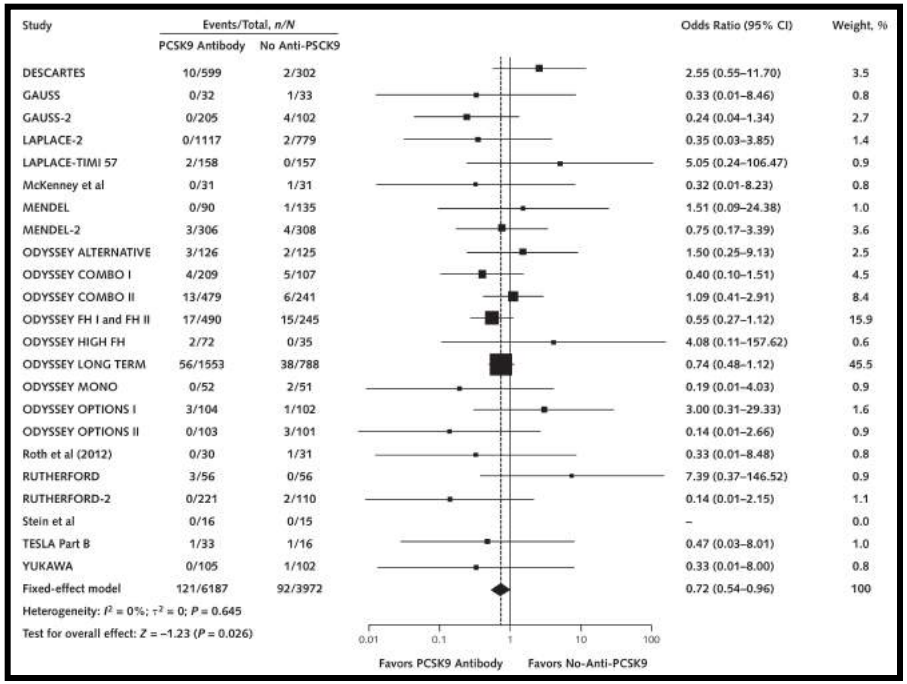
Lp(a) percentage of change from baseline



Ann Intern Med Jul 7, 2015;163:40-51

Effects of PCSK9 mAb in adults with hypercholesterolemia

Increase in CPK levels



Study	Events/Total, *n/N*		Odds Ratio (95% CI)	Weight, %
	PCSK9 Antibody	No Anti-PSCK9		
DESCARTES	10/599	2/302	2.55 (0.55–11.70)	3.5
GAUSS	0/32	1/33	0.33 (0.01–8.46)	0.8
GAUSS-2	0/205	4/102	0.24 (0.04–1.34)	2.7
LAPLACE-2	0/1117	2/779	0.35 (0.03–3.85)	1.4
LAPLACE-TIMI 57	2/158	0/157	5.05 (0.24–106.47)	0.9
McKenney et al	0/31	1/31	0.32 (0.01-8.23)	0.8
MENDEL	0/90	1/135	1.51 (0.09–24.38)	1.0
MENDEL-2	3/306	4/308	0.75 (0.17–3.39)	3.6
ODYSSEY ALTERNATIVE	3/126	2/125	1.50 (0.25–9.13)	2.5
ODYSSEY COMBO I	4/209	5/107	0.40 (0.10–1.51)	4.5
ODYSSEY COMBO II	13/479	6/241	1.09 (0.41–2.91)	8.4
ODYSSEY FH I and FH II	17/490	15/245	0.55 (0.27–1.12)	15.9
ODYSSEY HIGH FH	2/72	0/35	4.08 (0.11–157.62)	0.6
ODYSSEY LONG TERM	56/1553	38/788	0.74 (0.48–1.12)	45.5
ODYSSEY MONO	0/52	2/51	0.19 (0.01–4.03)	0.9
ODYSSEY OPTIONS I	3/104	1/102	3.00 (0.31–29.33)	1.6
ODYSSEY OPTIONS II	0/103	3/101	0.14 (0.01–2.66)	0.9
Roth et al (2012)	0/30	1/31	0.33 (0.01–8.48)	0.8
RUTHERFORD	3/56	0/56	7.39 (0.37–146.52)	0.9
RUTHERFORD-2	0/221	2/110	0.14 (0.01–2.15)	1.1
Stein et al	0/16	0/15	–	0.0
TESLA Part B	1/33	1/16	0.47 (0.03–8.01)	1.0
YUKAWA	0/105	1/102	0.33 (0.01–8.00)	0.8
Fixed-effect model	121/6187	92/3972	0.72 (0.54–0.96)	100

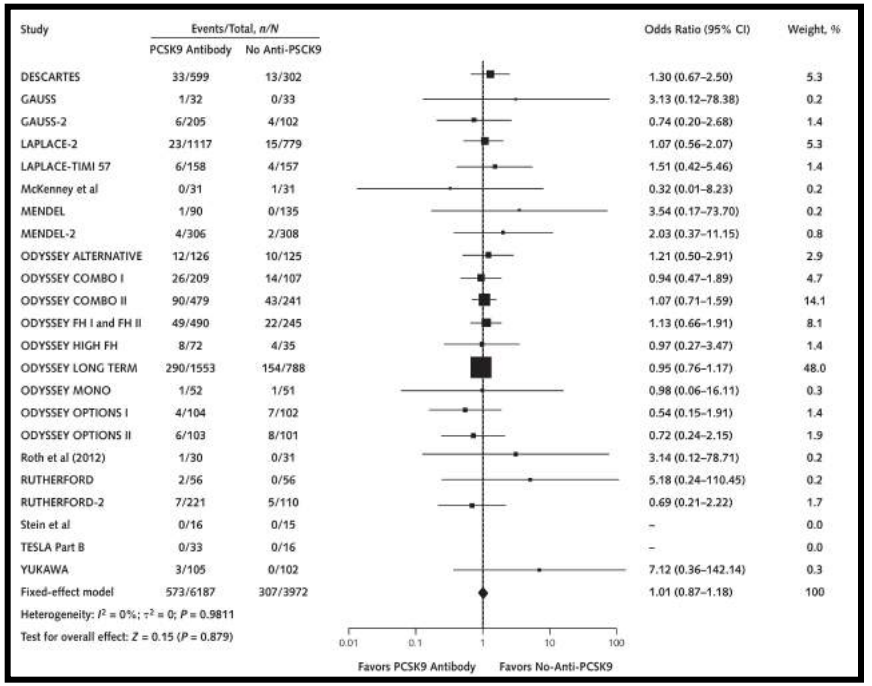
Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.645$

Test for overall effect: $Z = -1.23$ ($P = 0.026$)

0.01 0.1 1 10 100

Favors PCSK9 Antibody Favors No-Anti-PSCK9

Serious adverse events



Study	Events/Total, *n/N*		Odds Ratio (95% CI)	Weight, %
	PCSK9 Antibody	No Anti-PSCK9		
DESCARTES	33/599	13/302	1.30 (0.67–2.50)	5.3
GAUSS	1/32	0/33	3.13 (0.12–78.38)	0.2
GAUSS-2	6/205	4/102	0.74 (0.20–2.68)	1.4
LAPLACE-2	23/1117	15/779	1.07 (0.56–2.07)	5.3
LAPLACE-TIMI 57	6/158	4/157	1.51 (0.42–5.46)	1.4
McKenney et al	0/31	1/31	0.32 (0.01–8.23)	0.2
MENDEL	1/90	0/135	3.54 (0.17–73.70)	0.2
MENDEL-2	4/306	2/308	2.03 (0.37–11.15)	0.8
ODYSSEY ALTERNATIVE	12/126	10/125	1.21 (0.50–2.91)	2.9
ODYSSEY COMBO I	26/209	14/107	0.94 (0.47–1.89)	4.7
ODYSSEY COMBO II	90/479	43/241	1.07 (0.71–1.59)	14.1
ODYSSEY FH I and FH II	49/490	22/245	1.13 (0.66–1.91)	8.1
ODYSSEY HIGH FH	8/72	4/35	0.97 (0.27–3.47)	1.4
ODYSSEY LONG TERM	290/1553	154/788	0.95 (0.76–1.17)	48.0
ODYSSEY MONO	1/52	1/51	0.98 (0.06–16.11)	0.3
ODYSSEY OPTIONS I	4/104	7/102	0.54 (0.15–1.91)	1.4
ODYSSEY OPTIONS II	6/103	8/101	0.72 (0.24–2.15)	1.9
Roth et al (2012)	1/30	0/31	3.14 (0.12–78.71)	0.2
RUTHERFORD	2/56	0/56	5.18 (0.24–110.45)	0.2
RUTHERFORD-2	7/221	5/110	0.69 (0.21–2.22)	1.7
Stein et al	0/16	0/15	–	0.0
TESLA Part B	0/33	0/16	–	0.0
YUKAWA	3/105	0/102	7.12 (0.36–142.14)	0.3
Fixed-effect model	573/6187	307/3972	1.01 (0.87–1.18)	100

Heterogeneity: $I^2 = 0\%$; $\tau^2 = 0$; $P = 0.9811$

Test for overall effect: $Z = 0.15$ ($P = 0.879$)

0.01 0.1 1 10 100

Favors PCSK9 Antibody Favors No-Anti-PSCK9

Ann Intern Med Jul 7, 2015;163:40-51

LDL-cholesterol and CV Risk

European Heart Journal Advance Access published March 31, 2015

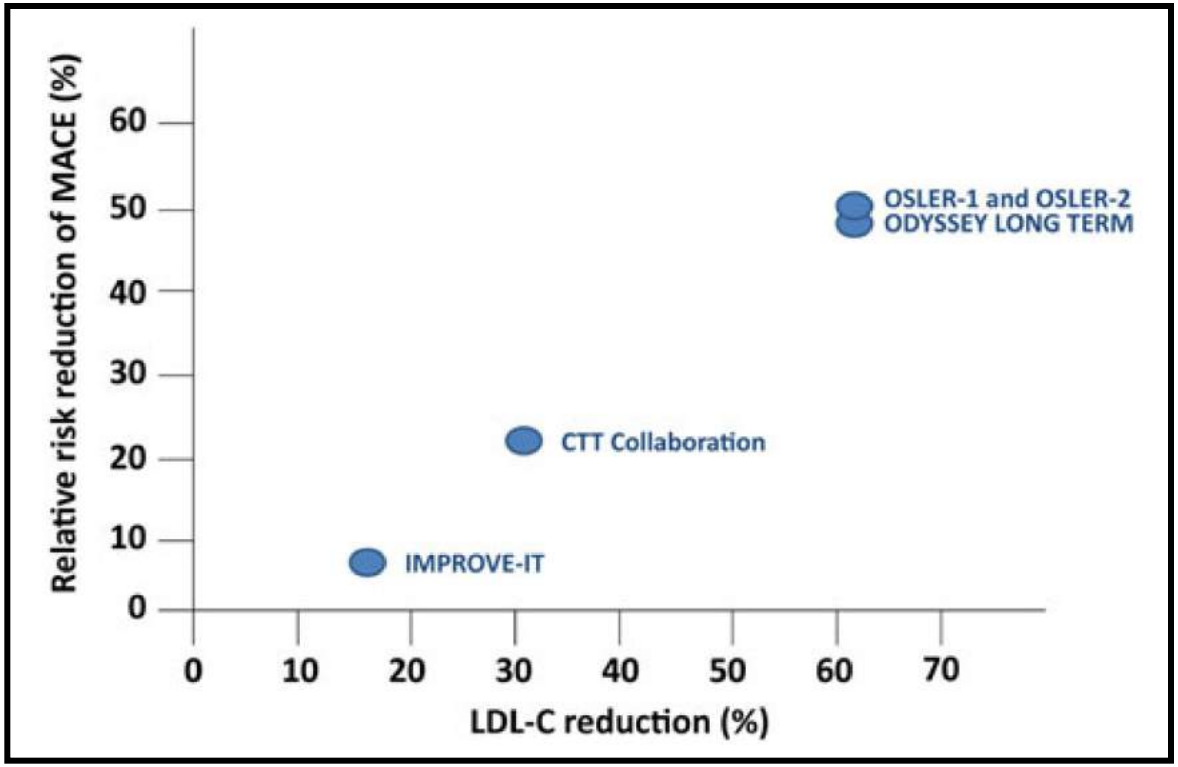
European Heart Journal
doi:10.1093/eurheartj/ehv056

EDITORIAL

Sweetless'n low LDL-C targets for PCSK9 treatment

Baris Gencer and François Mach*

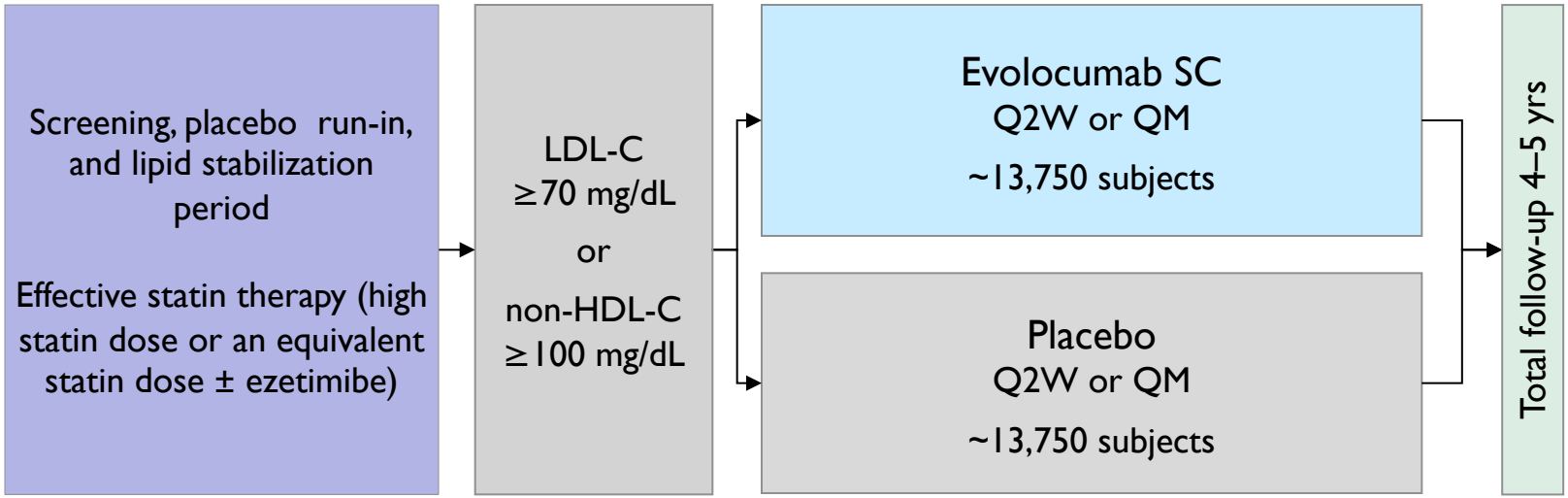
Cardiology Division, Department of Specialties in Medicine, Geneva University Hospitals, Switzerland



Eur Heart J 2015:36:1146-8

FOURIER: cardiovascular outcomes with PCSK9 inhibition in subjects with elevated CV risk

28,500 patients with clinically evident CVD (prior MI, stroke or PAD)
Age 40 to 85 years, ≥1 other high-risk features



Primary endpoint: CV death, MI, hospitalization for UA, stroke, coronary revascularization

CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral arterial disease; Q2W, once every 2 weeks; QM, once monthly; SC, subcutaneous; UA, unstable angina.

PCSK9 inhibitors review

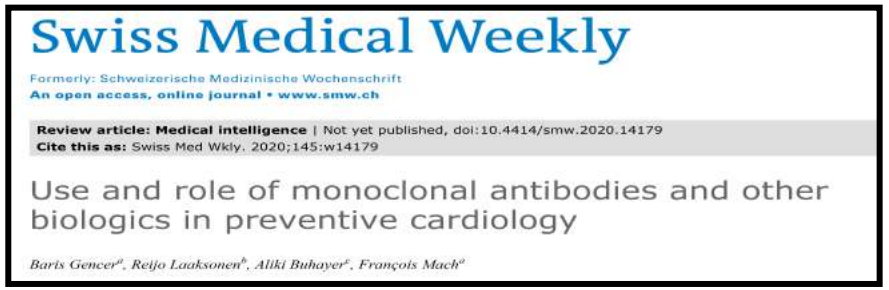

REVIEW ARTICLE. MEDICAL INTELLIGENCE

Inhibition of PCSK9 is a promising therapeutic option for the lowering of LDL-C levels

PCSK9 inhibitors

Baris Gencer[a], Gilles Lambert [b,c], François Mach[a]

Swiss Med Wkly April 2015;145:w14094


Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Medical intelligence | Not yet published, doi:10.4414/smw.2020.14179

Cite this as: Swiss Med Wkly. 2020;145:w14179

Use and role of monoclonal antibodies and other biologics in preventive cardiology

Baris Gencer[a], Reijo Laaksonen[b], Aliki Buhayer[c], François Mach[a]

Swiss Med Wkly November 2015;145:w14179


Inhibiteurs de la PCSK9 : un nouveau traitement pour l'hypercholestérolémie

Dr BARIS GENCER[a], Prs NICOLAS RODONDI[b] et FRANÇOIS MACH[a]

Rev Med Suisse 2016; 12: 440-4

RMS March 2016;12:440-4


Current Opinion for Swiss Medial Weekly

Statin-associated muscle symptoms: impact on current and future therapies

Baris Gencer, MD[1]; Nicolas Rodondi, MD, MAS[2]; François Mach, MD[1]

Swiss Med Wkly 2016; in press

Dyslipidémies - Guidelines

European Heart Journal Advance Access published August 27, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw272

ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

Dyslipidémies traitements

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C	115, 116

PCSK9, indications et limites

European Heart Journal Advance Access published October 27, 2016

European Heart Journal (2016) 0, 1–11
doi:10.1093/eurheartj/ehw480

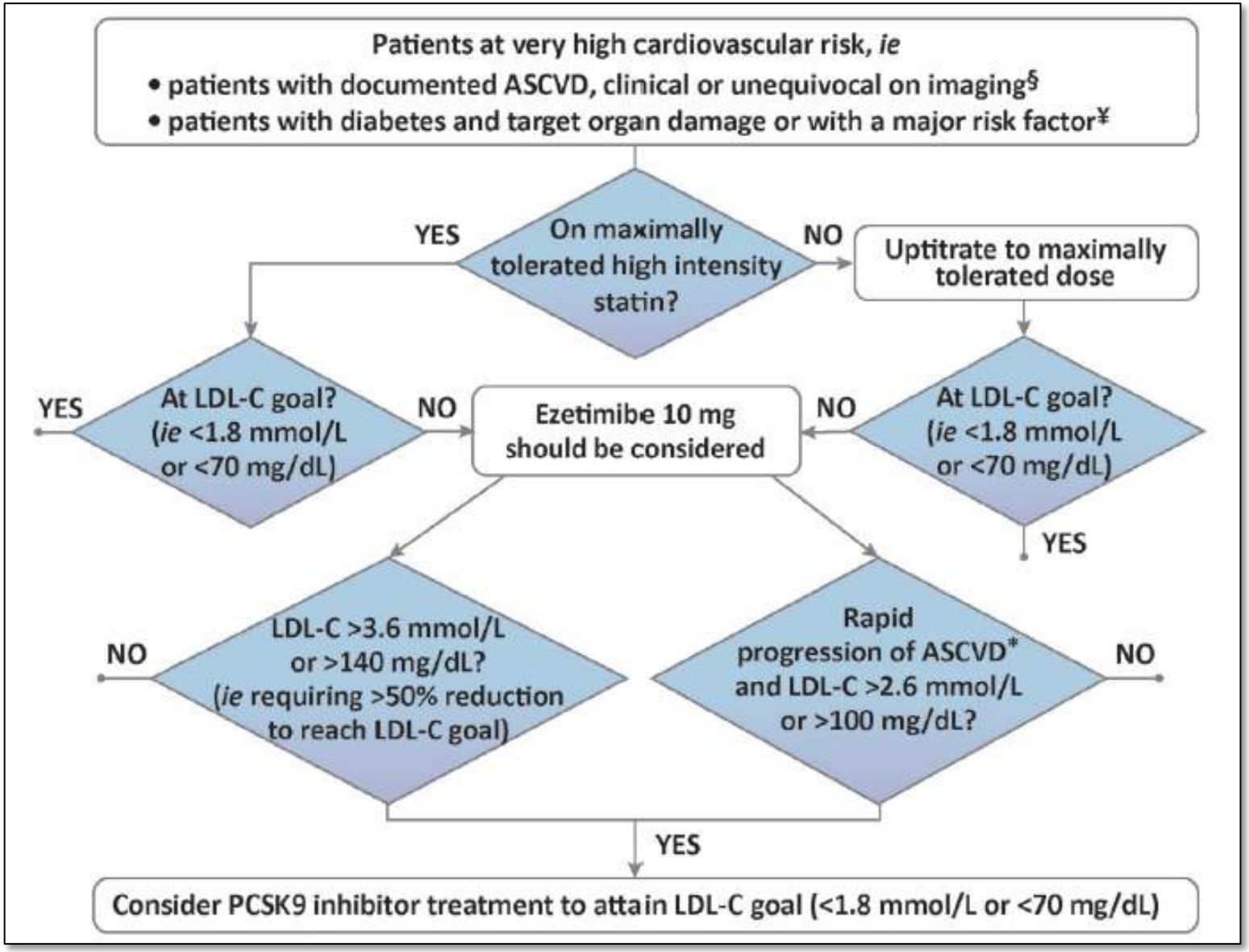
CURRENT OPINION

European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk

Ulf Landmesser[1]*†, M. John Chapman[2†], Michel Farnier[3], Baris Gencer[4], Stephan Gielen[5], G. Kees Hovingh[6], Thomas F. Lüscher[7], David Sinning[1], Lale Tokgözoğlu[8], Olov Wiklund[9], Jose Luis Zamorano[10], Fausto J. Pinto[11], and Alberico L. Catapano[12] on behalf of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

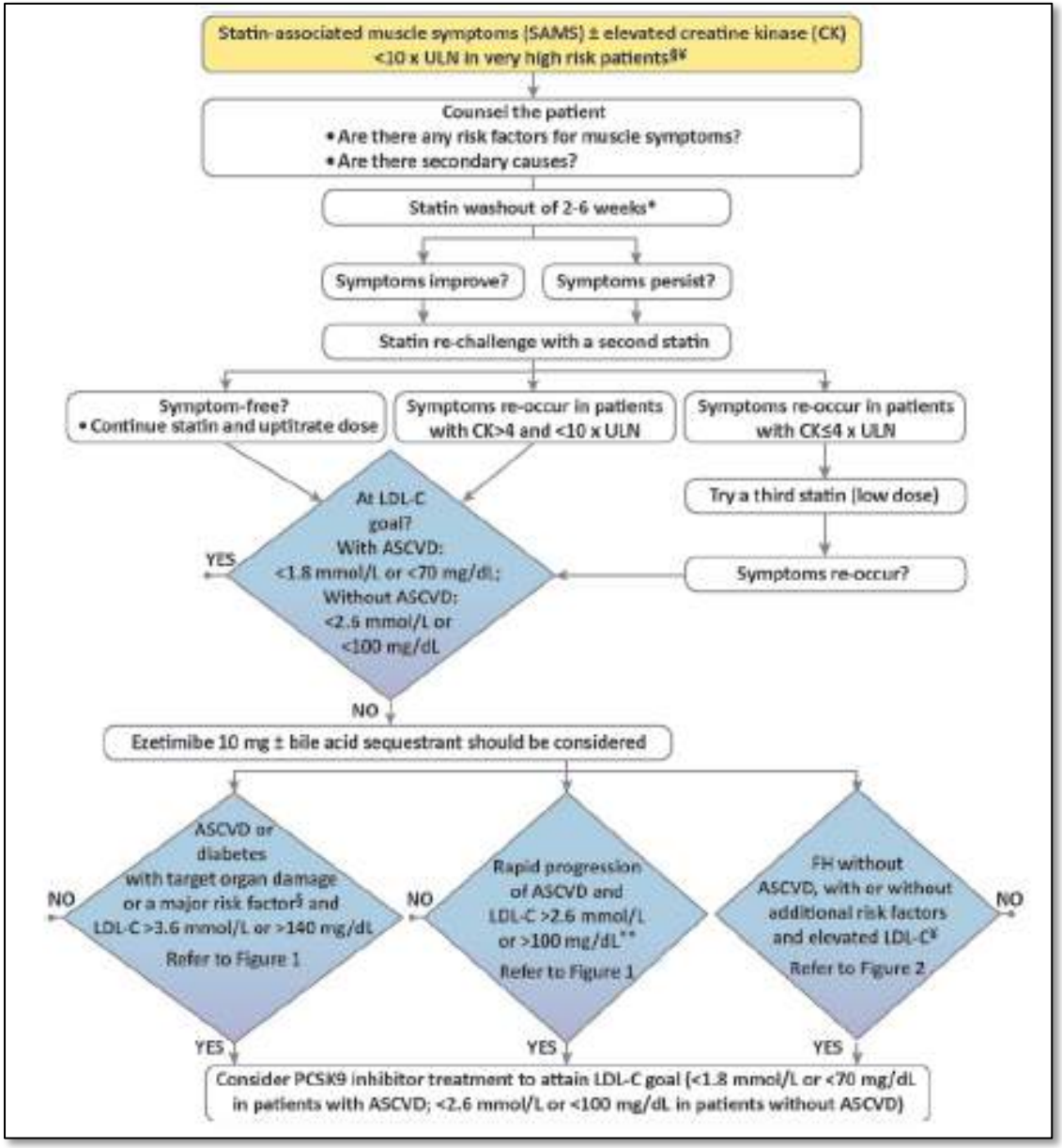
Eur Heart J 2016; October 27, 2106

PCSK9, indications et limites



Eur Heart J 2016; October 27, 2106

PCSK9, indications et limites



Eur Heart J 2016; October 27, 2106

Therapeutic algorithm for the treatment of hypercholesterolemia

Logo hospital

Determination of the overall cardiovascular risk via SCORE/AGLA
Determination of total cholesterol, LDL-, HDL cholesterol and triglycerides (TG)

Very high risk

- documented CVD, clinical or unequivocal on imaging (e.g. carotic plaque)
- type-2 DM or type-1 DM with additional risk factors/organ damage (e.g. proteinuria)
- Severe CKD (GFR < 30 mL/min/1.73m²)
- calculated SCORE risk ≥ 10%

High risk

- markedly elevated single risk factors, (in particular cholesterol >8 mmol/L, family history of dyslipidaemias/ hypercholesterolemia or BP>180/110 mmHG)
- Moderate CKD (GFR 30 – 59 mL/min/1.73m²)
- calculated SCORE ≥ 5% to < 10%, AGLA risk > 20 %

Low to moderate risk

- Patients with calculated SCORE <1% or ≥ 1% to <5 % for 10-year risk of fatal CVD
- AGLA risk for 10-year risk of cardiovascular event ≤ 20 %

start max. tolerated high-intensity statins immediately in all high and very high risk patients (Atorva 40/80 mg or Rosuva 20/40 mg)

Monitoring of LDL cholesterol after 4 – 6 weeks, no later than 3 months

LDL-C target value
< 1.8 mmol/l,
or reduction by 50% if LDL-C > 1.8 ≤ 3.6 mmol/l

LDL-C target value
< 2.6 mmol/l,
or reduction by 50% if LDL-C ≥ 2.6 ≤ 5.2 mmol/l

LDL-C target value
< 3 mmol/l

If LDL cholesterol lies above the given target value, then
(1) **reinforce lifestyle adaptation** (nutrition and exercise) and (2) **increase statin therapy to max. tolerated dose**

if not at goal with max. tolerated statin, start therapy with ezetimibe

If LDL cholesterol lies above the given target value, then
(1) **reinforce lifestyle adaptation** (nutrition and exercise) and (2) **consider statin therapy**

LDL-C ≥ target value

consider therapy with PCSK9-Inhibitors

LDL-C ≥ target value

consider Lipidapharesis

LDL-C < target value

Continue therapy, monitor LDL-C level every year

LDL-C < target value

Continue therapy, monitor LDL-C level every year

Logo AGLA

LDL-C > 4.9 mmol/l

Familial Hypercholesterolemia should be considered,
screen according to **Dutch Lipid Clinic Network criteria**

References:
http://www.agla.ch/
Catapano, A. L. *et al.* 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur. Heart J.* http://dx.doi.org/10.1093/eurheartj/ehw272
Austin, M. A., Hutter, C. M., Zimmern, R. L. & Humphries, S. E. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. *Am. J. Epidemiol.* **160**, 407–20 (2004).

Abbreviations:
CVD-coronary vascular disease; ESC-European Society of Cardiology; CKD-Congenital kidney disease; GFR-Glomerular Filtration rate; DM- Diabetes mellitus

Dyslipidémies hypercholestérolémie famillliale

Table 21 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia[311]

Criteria	Points
1) Family history	
First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or	
First-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or	
children <18 years of age with LDL-C above the 95th percentile (see 9.1.2.3)	2
2) Clinical history	
Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels	
LDL-C ≥ 8.5 mmol/L (325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the LDLR, apoB or PCSK9 gene	8
Choose only one score per group, the highest applicable Diagnosis (diagnosis is based on the total number of points obtained)	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

Table 22 Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

Recommendations	Class[a]	Level[b]
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (100 mg/dL) or in the presence of CVD <1.8 mmol/L (70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	IIa	C
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance.	IIa	C
In children, testing is recommended from age 5 years, or earlier if homozygous FH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

SPUM Inflammation – acute coronary syndromes

Prevalence of Familial Hypercholesterolemia in CH

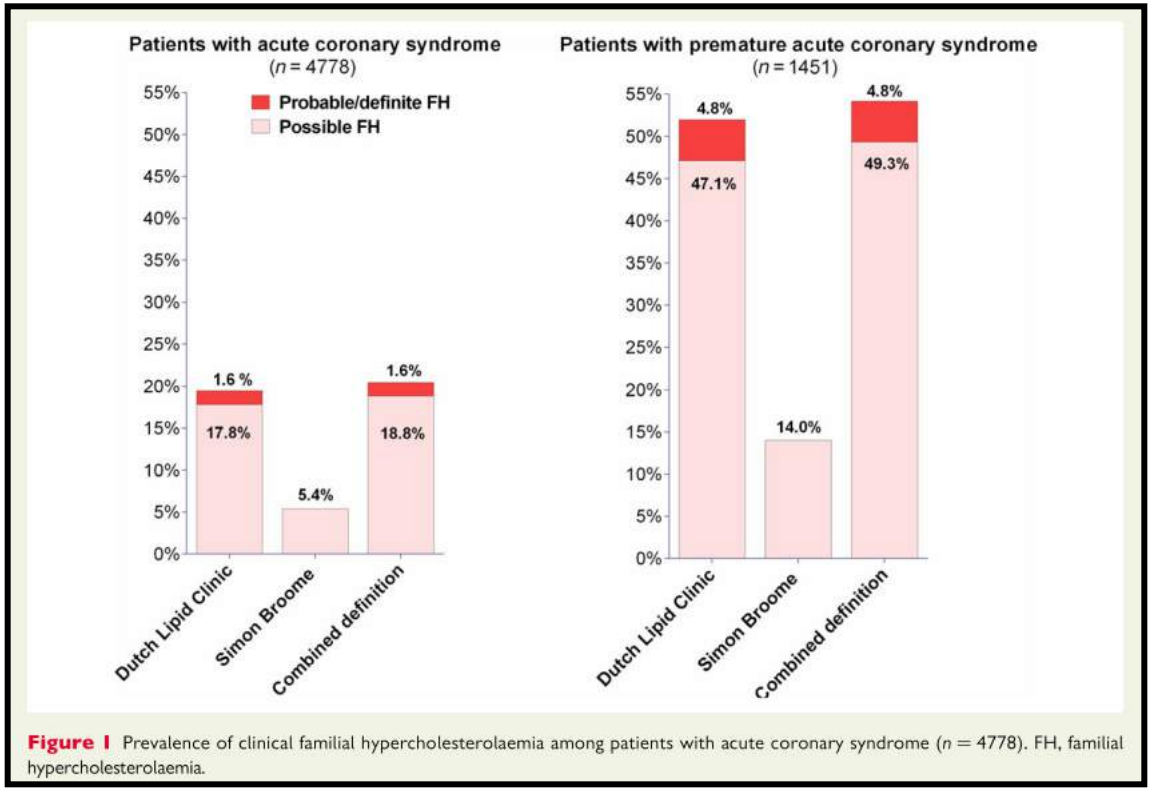


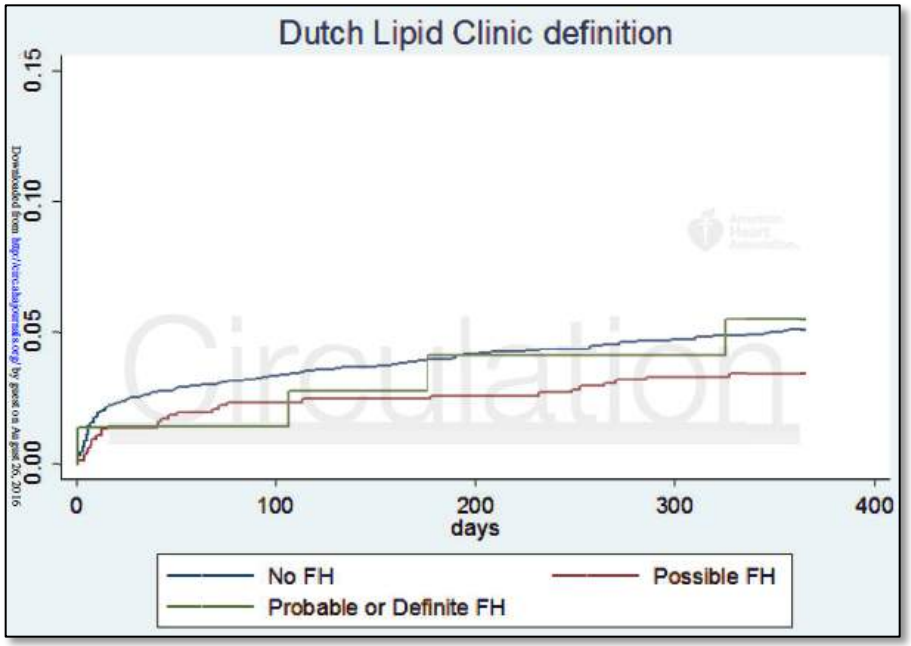
Figure 1 Prevalence of clinical familial hypercholesterolaemia among patients with acute coronary syndrome ($n = 4778$). FH, familial hypercholesterolaemia.

Eur Heart J July 2015;36-2438

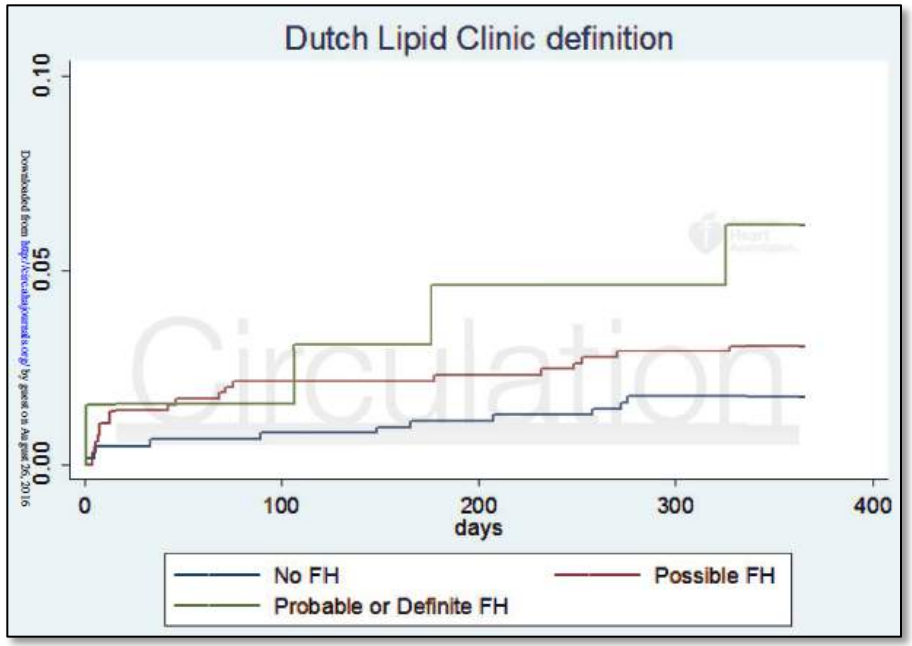
SPUM Inflammation – acute coronary syndromes

Prognosis of Familial Hypercholesterolemia in CH

Incidence of recurrent coronary events after ACS, by presence of FH (n=4'534)



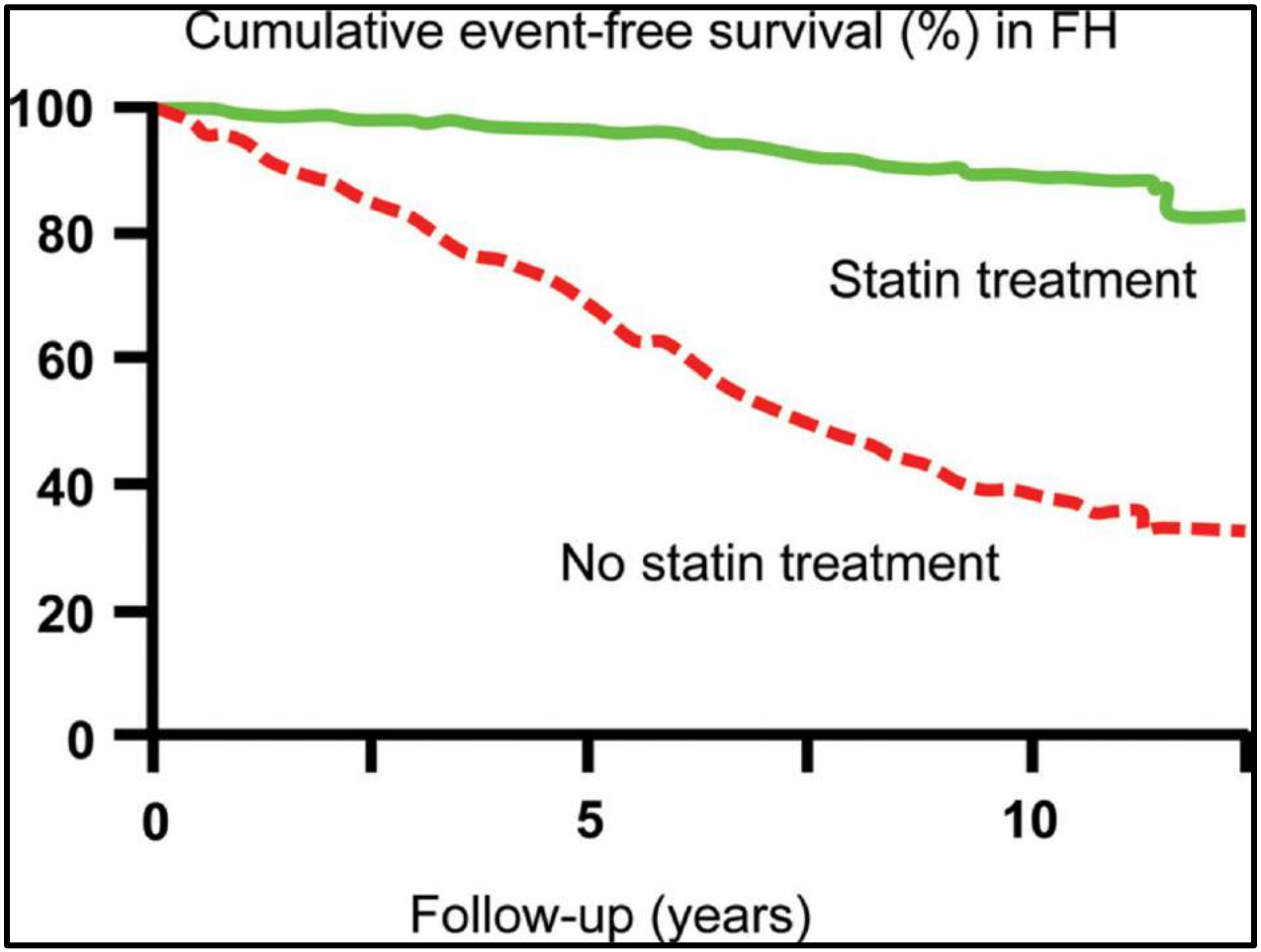
Incidence of recurrent coronary events in young patients with premature ACS, by presence of FH (n=1'369)



Nanchen D. et al; *ESC abstract* 2016; *Circulation* 2016; online

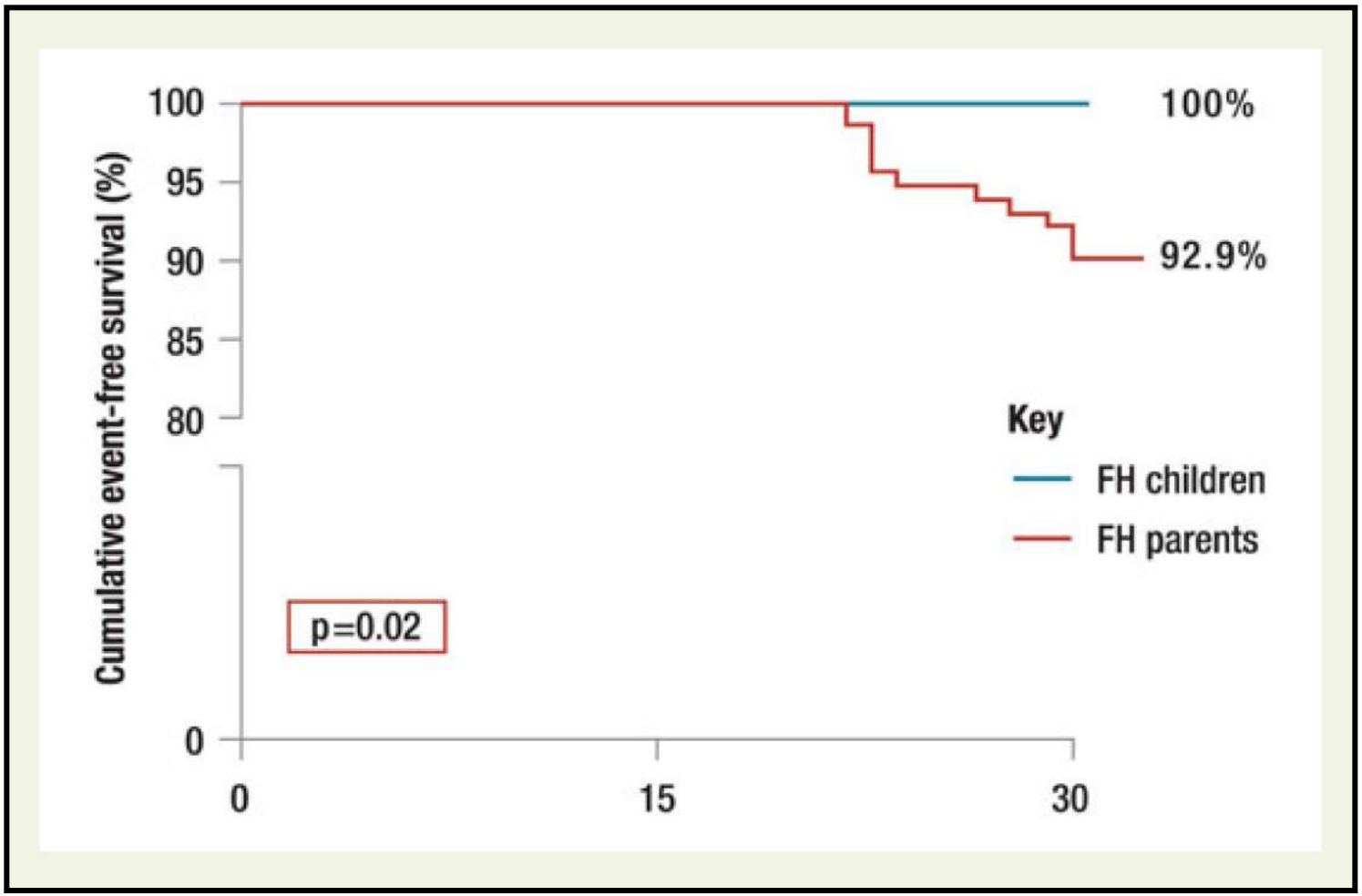
Treatment of Familial Hypercholesterolemia

Kaplan–Meier curve estimates of cumulative CHD-free survival among individuals with familial hypercholesterolemia according to statin treatment



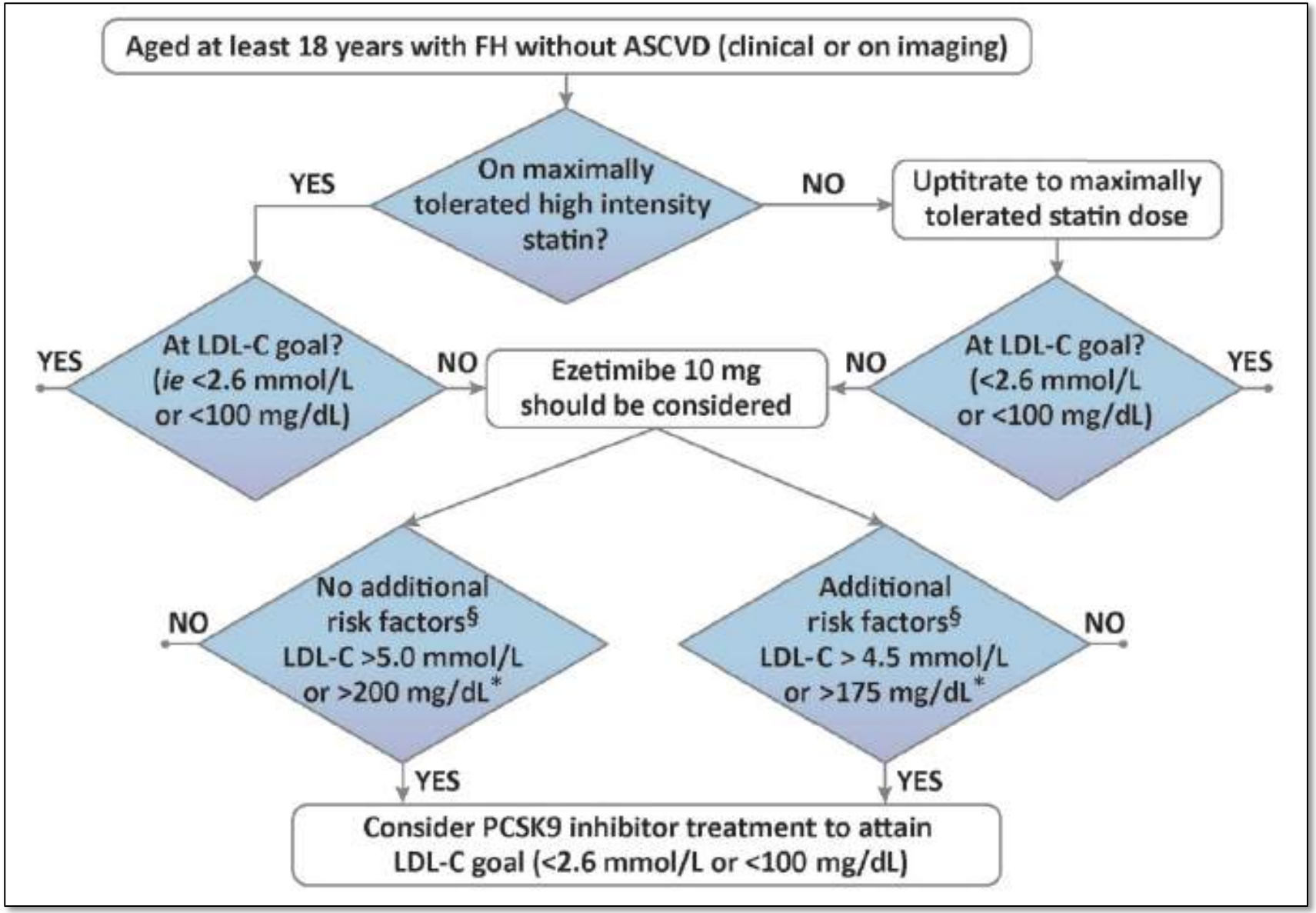
Eur Heart J 2013;34:3478

Treatment of Familial Hypercholesterolemia



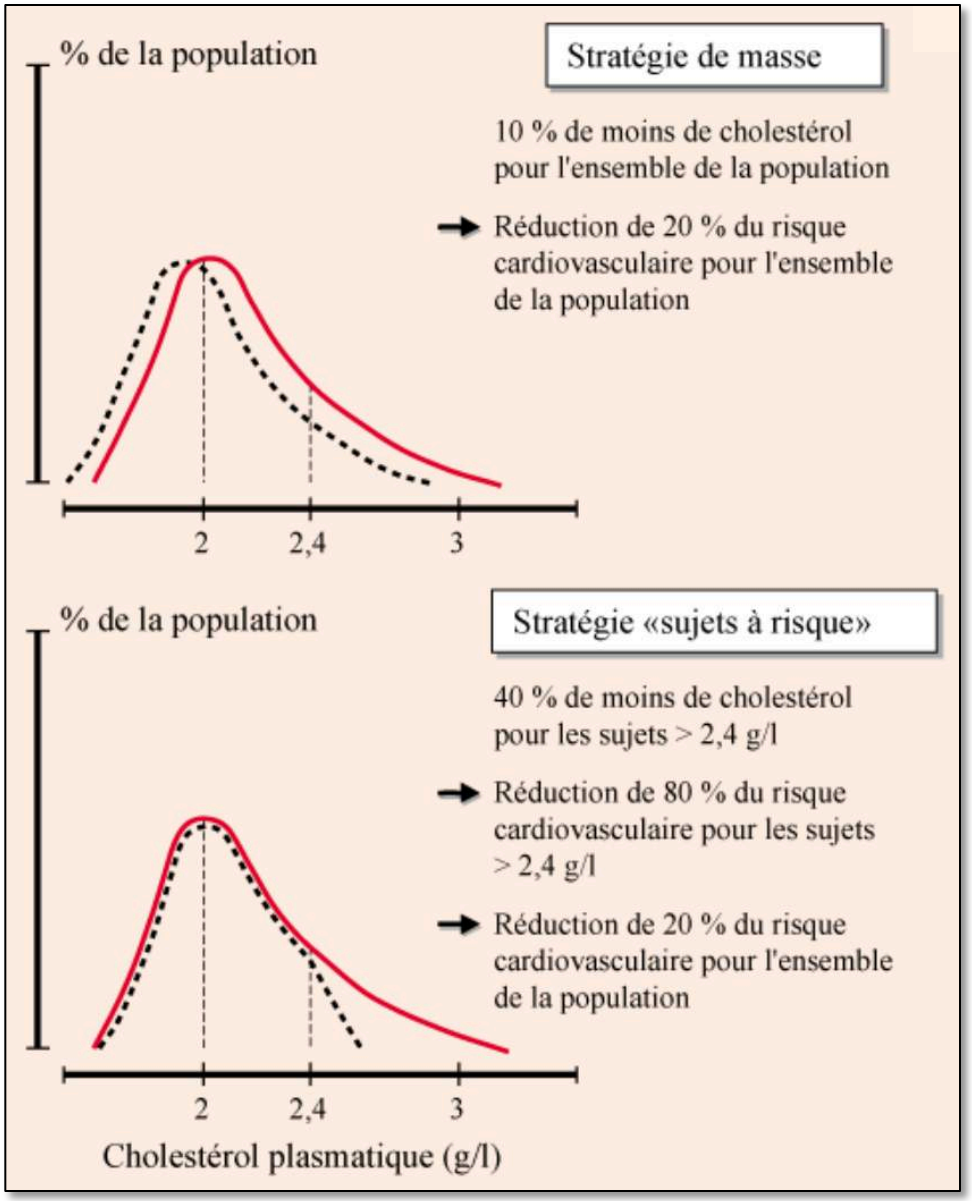
Euro Heart J 2015;36,2425

PCSK9, indications et limites



Eur Heart J 2016; October 27, 2106

Traiter le cholestérol – les évidences



A practical approach to reach LDL-C goal

ESC pocket guidelines:

attainable with
statin + ezetimibe

attainable with
statin monotherapy

Table Percentage reduction of LDL-C requested to achieve goals as a function of the starting value

STARTING LDL-C		% REDUCTION TO REACH LDL-C		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.5 mmol/ (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

Hôpitaux Universitaires Genève

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CH – 1211 Genève 14

COMMUNIQUE DE PRESSE

Genève, le 6 novembre 2016

Cholestérol et maladies cardiovasculaires

Les statines dans le traitement du cholestérol sauvent des vies

Ces derniers temps, un débat public a eu lieu sur les statines et leur efficacité dans le traitement du cholestérol. Certains médias s'en sont d'ailleurs fait l'écho, ce qui a pour effet d'inquiéter certains patients, qui s'interrogent aujourd'hui sur l'opportunité de leur traitement. Les Hôpitaux universitaires de Genève (HUG) et le Pr François Mach, Chef du service de cardiologie des HUG, sont également questionnés sur le sujet par leurs patients et souhaitent préciser ce qui suit.

Selon le Pr François Mach et conformément à l'avis de la société Suisse de Cardiologie, aucun autre médicament en médecine préventive ne possède un niveau de preuves d'efficacité clinique aussi élevé que les statines. Elles allongent l'espérance de vie des patients à risque, diminuent les événements cardiovasculaires (infarctus et AVC notamment) et ont un risque d'effets indésirables limité largement compensé par l'ampleur des bénéfices. Nier les bienfaits d'un traitement de statine et leur impact sur l'espérance de vie, c'est à la fois malhonnête (en refutant les faits et évidences scientifiques) mais également dangereux pour les patients qui, bien que de bonne foi, pourraient arrêter leur traitement suite à de la désinformation). Nier les progrès thérapeutiques, porter la suspicion sur les médecins, c'est aussi ignorer l'amélioration incontestable du pronostic cardiovasculaire. Depuis 1990, le taux de mortalité par crise cardiaque a baissé de 40% en moyenne dans les pays membres de l'OCDE, souligne le Panorama de la santé 2013 publié par l'organisation. Les décès par AVC ont pour leur part été divisés par deux. En Suisse, l'effet est tout aussi spectaculaire, avec une diminution de la mortalité cardiovasculaire d'environ 30% pour les années 1998 à 2007.

Cholestérol/statines – conclusions

<u>Oui,</u> le cholestérol est un facteur de risque CV,

<u>Oui,</u> le traitement de statine diminue le risque de futur événements CV,

<u>Oui,</u> le traitement de statine a des effects secondaires, bénins,

<u>Oui, lorsque bien indiqué, le traitement de statine est, très largement, coût-bénéfique,</u>

Les PCSK9 mAb sont des médicaments très puissants pour permettre d'atteindre les valeurs cibles, mais ne doivent être préscrits que dans certaines indications, et chez des patients à très haut risque CV.