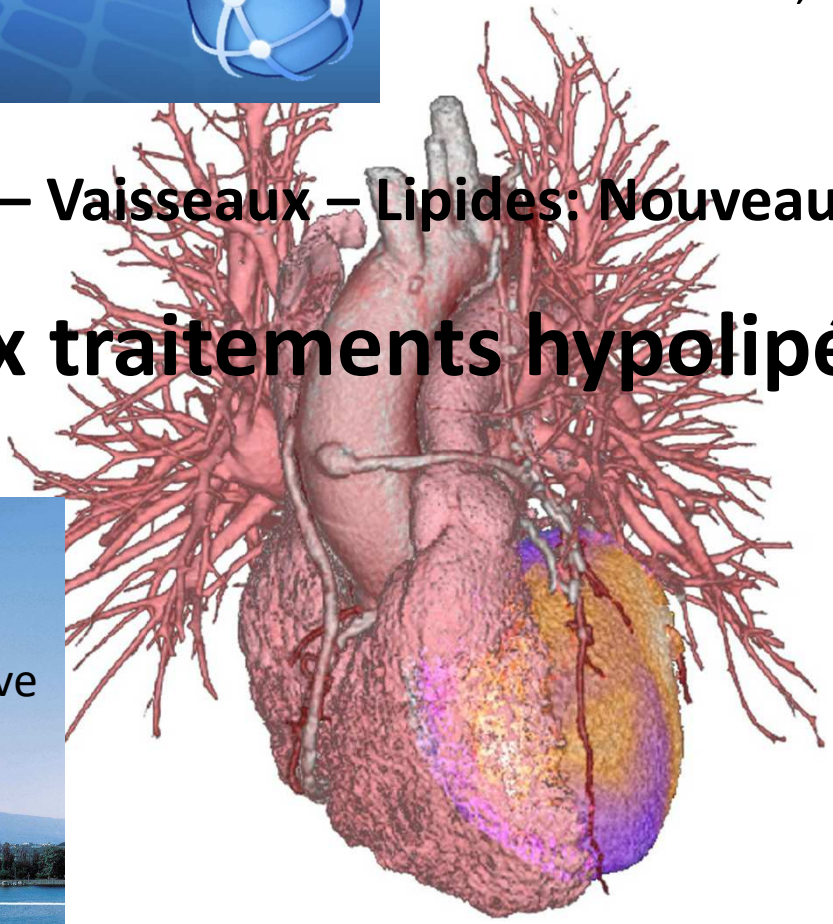
REMED
Réseau de Médecins - Genève

FER, Genève, le 3 mai 2022



Reins – Vaisseaux – Lipides: Nouveautés

Nouveaux traitements hypolipémiants

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Service de Cardiologie

HUG Hôpitaux Universitaires Genève

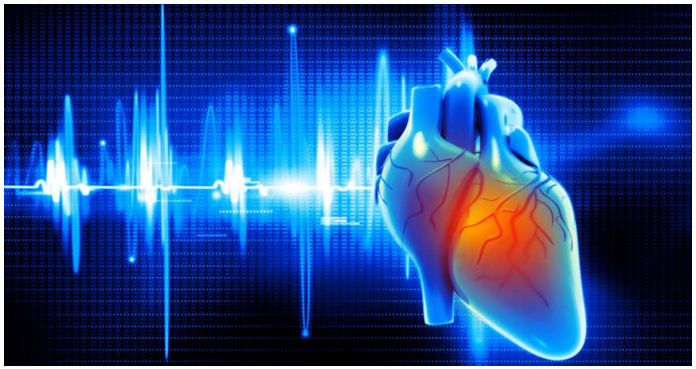
UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

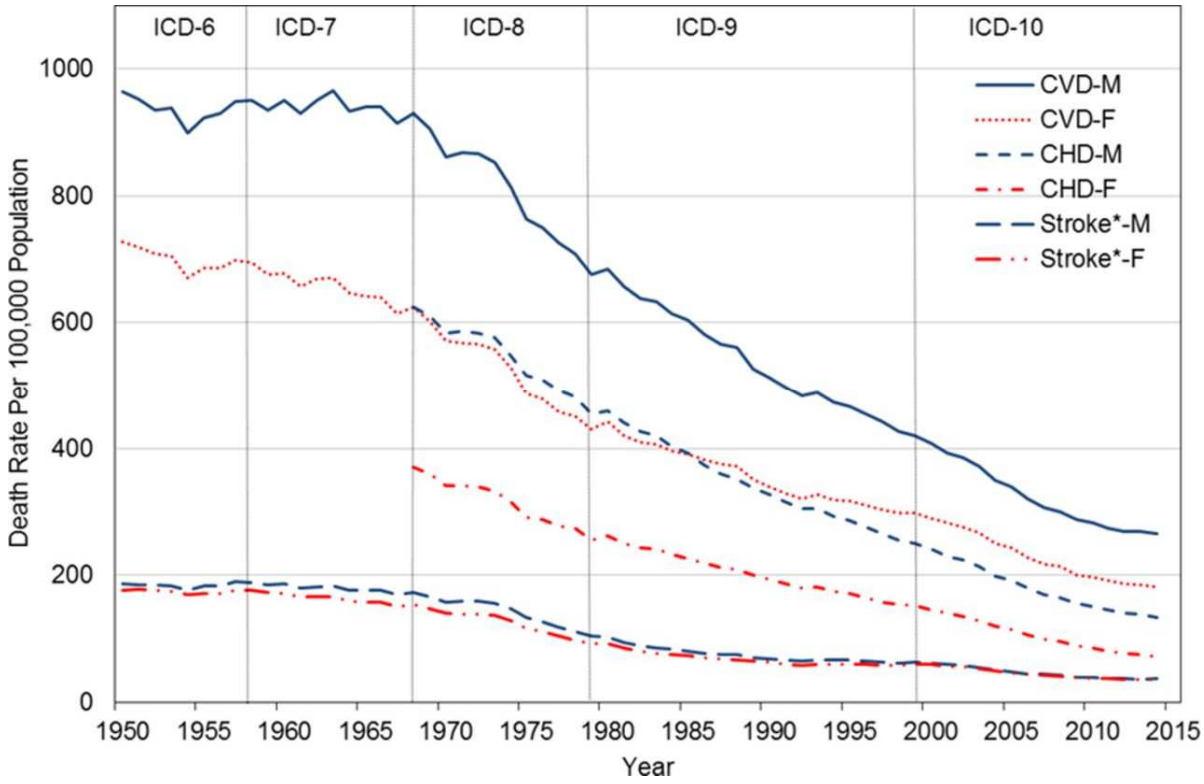
Aucun conflit d’intérêt

Tous mes honoraires pour conférences ou conseils scientifiques sont versés à la Fondation GEcor ou au Département de Médecine des HUG.

Le service de cardiologie a reçu des financements de firmes pharmaceutiques pour la recherche clinique, toujours via des contrats signés par le Département de Médecine des HUG.

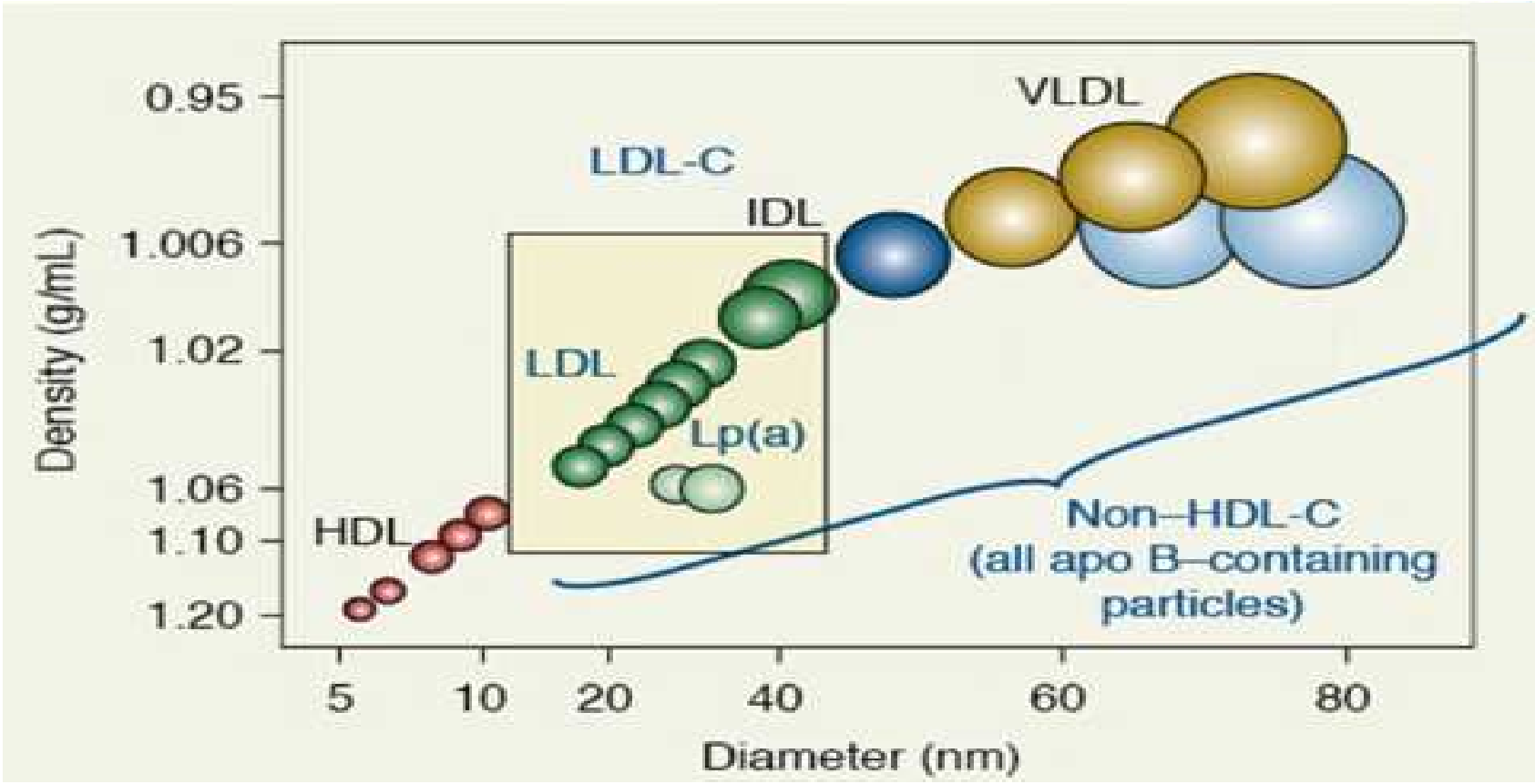
Cardiovascular Prevention





Maladies cardiovasculaires

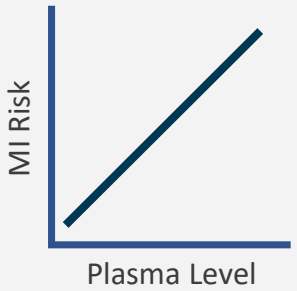
Characteristics of lipoproteins



Clear relationship between LDL-C and risk of CV events

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

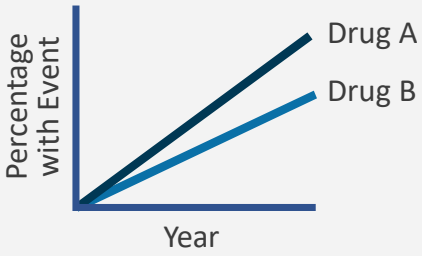
Epidemiology

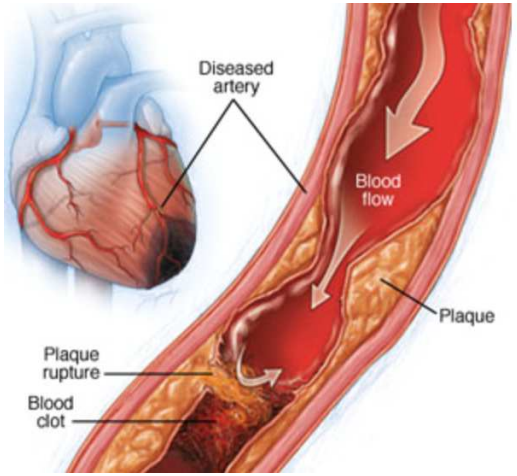


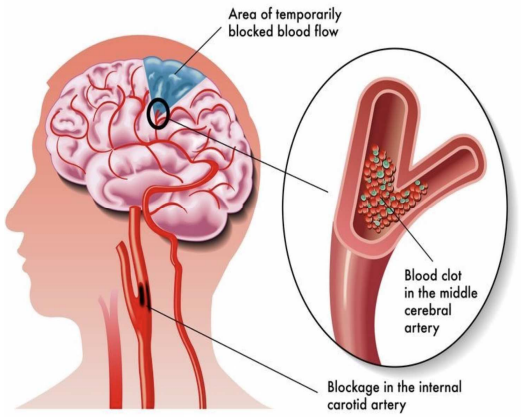
Human Genetics

Experimental

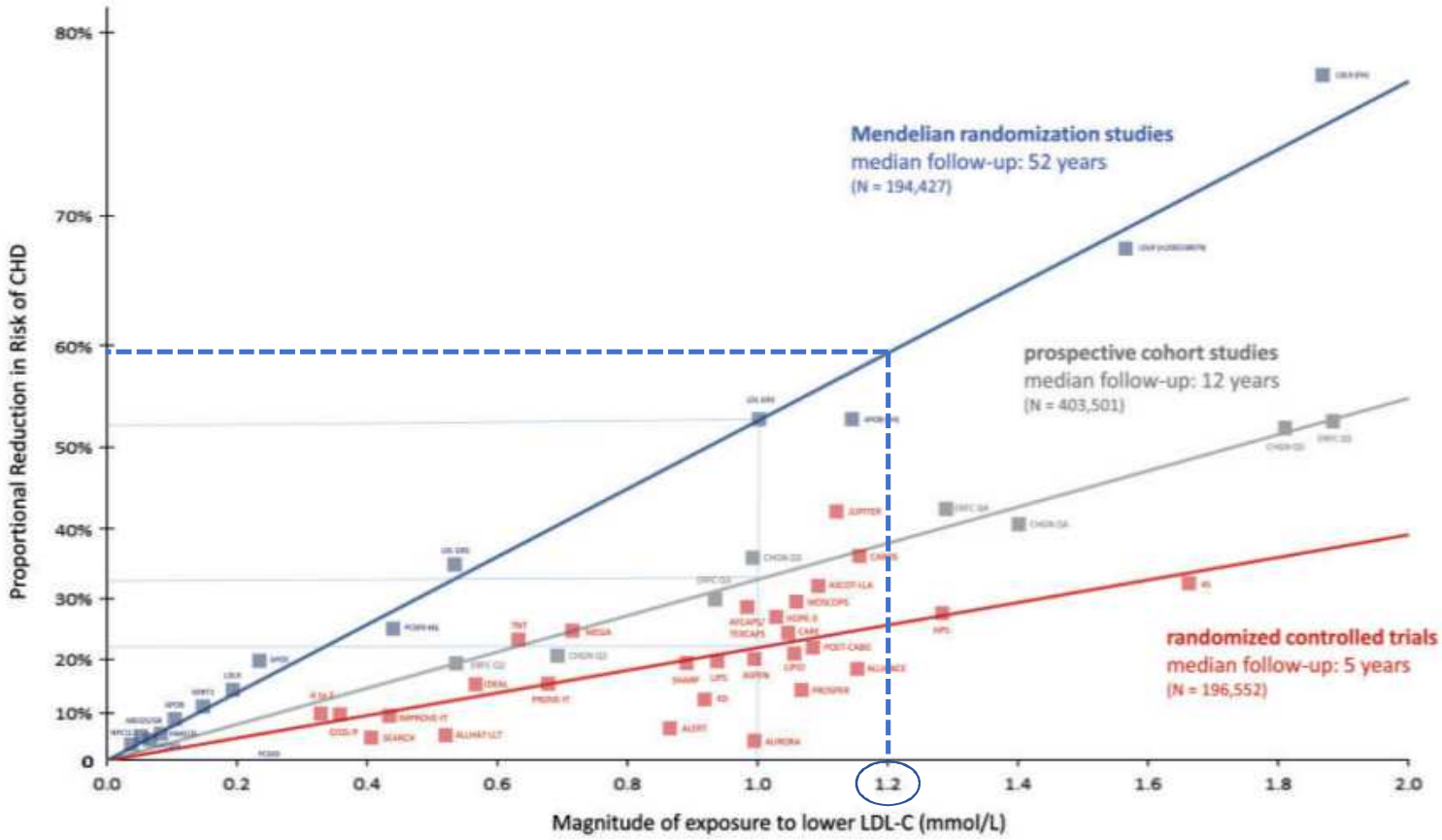
Therapy







Time-Exposure to Low LDL-C



Eur Heart J 2017;38:2459

2019 ESC/EAS Dyslipidemia Guidelines

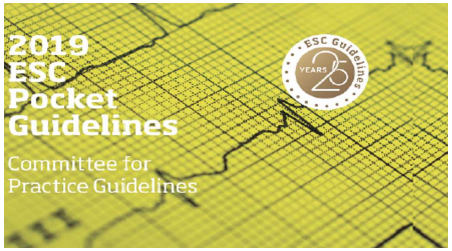
ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

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

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (Belgium), Victoria Delgado (Netherlands), Brian A. Ference (United Kingdom), Ian M. Graham (Ireland), Alison Halliday (United Kingdom), Ulf Landmesser (Germany), Borislava Mihaylova (United Kingdom), Terje R. Pedersen (Norway), Gabriele Riccardi[1] (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen[1] (Finland), Lale Tokgozoglu[1] (Turkey), Olov Wiklund[1] (Sweden)



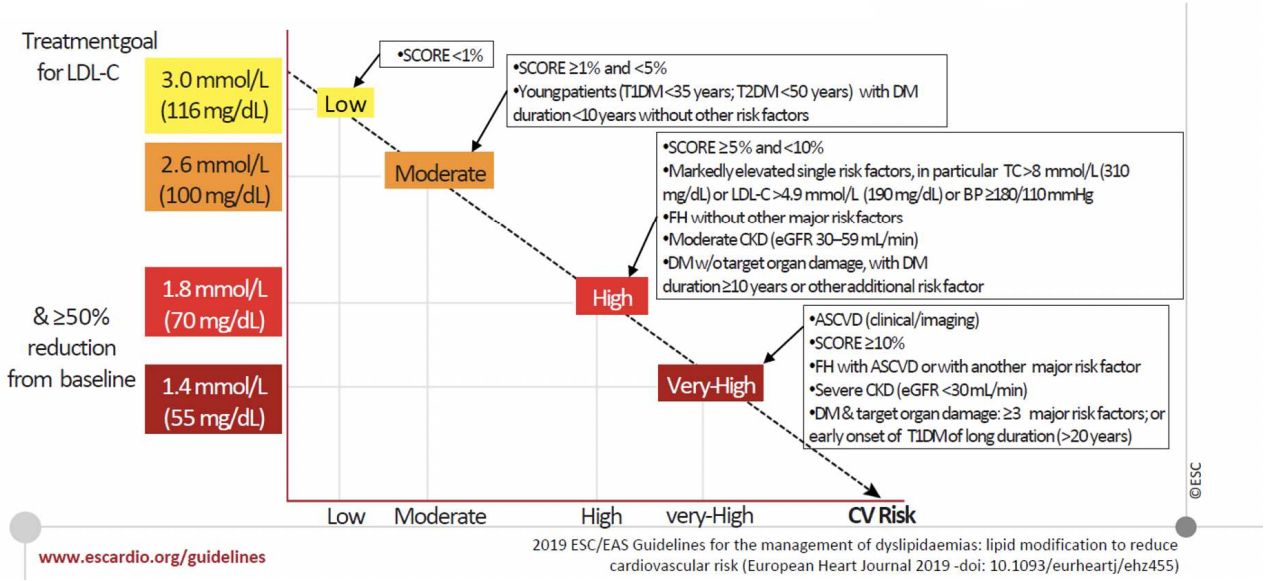
DYSLIPIDAEMIAS
Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk

ESC European Society of Cardiology

EAS

Treatment goals for LDL-C across categories of total cardiovascular disease risk

EAS ESC European Society of Cardiology



www.escardio.org/guidelines

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

Eur Heart J 2020;41:111

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;41:111-188

DA VINCI study demonstrates current gaps in reaching 2016 and 2019 ESC/EAS LDL-C goals

Overall, 54% attained overall risk-based 2016 goal

- Low risk: 63%; moderate risk: 75%; high risk: 63%; very high risk: 39%

Only **33%** attained overall **2019 goal**

In patients with established **ASCVD**, **2019 goal attainment was approximately half that of 2016** (18% vs 39%, respectively)

Potential reasons for failure to achieve ESC/EAS guideline recommended LDL-C values

- Lack of HCP familiarity with guidelines
- High cost of medications such as PCSK9 mAb inhibitors
- Patient reluctance to be treated with high-intensity LLT
- Concern about statin-related AEs

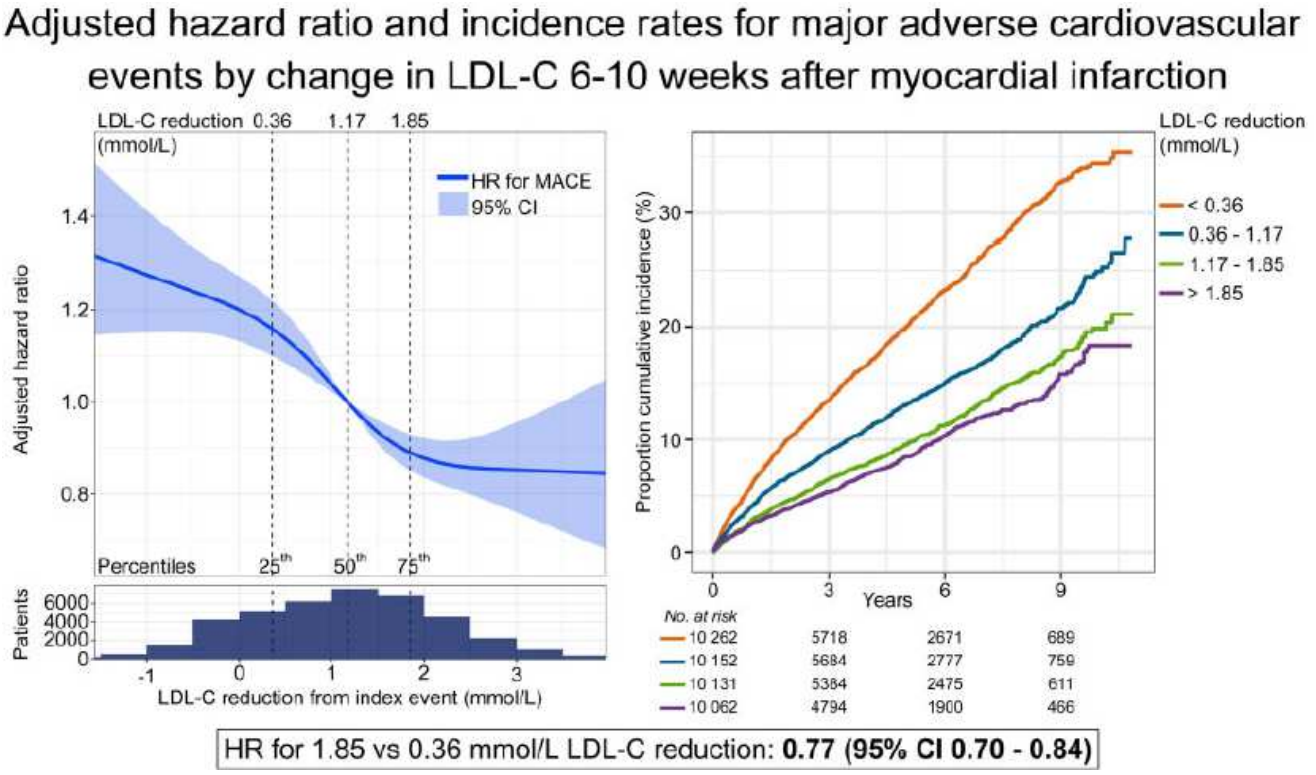
The authors concluded that **"even with optimized statins, greater utilization of non-statin LLT is likely needed to reduce these gaps for patients at highest risk"**

Eur J Prev Cardiol August 2020

LDL-C: should we go lower after ACS ?

Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study

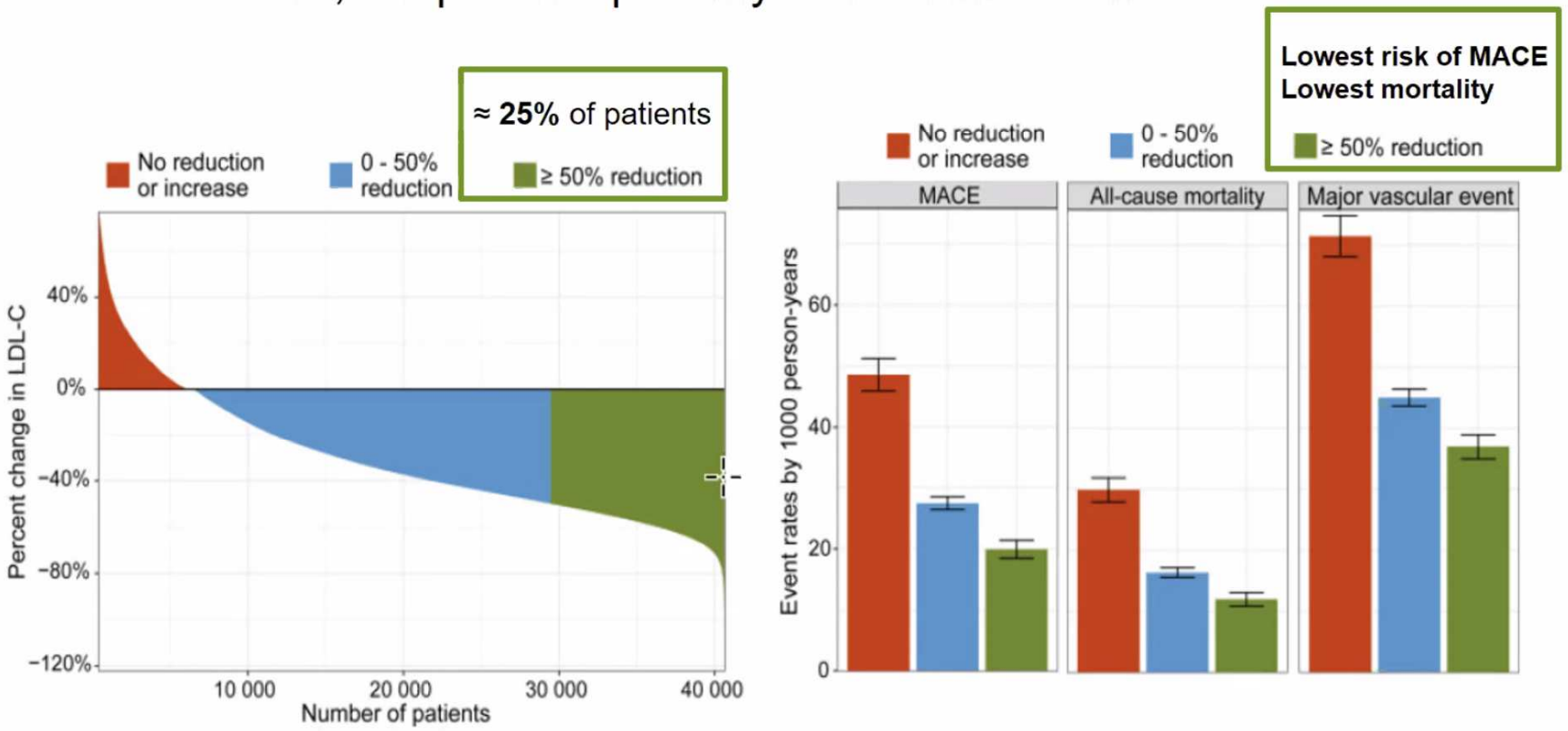
Jessica Schubert [1]*, Bertil Lindahl [1,2], Håkan Melhus [1], Henrik Renlund [2], Margrét Leosdottir [3,4], Ali Yari [5], Peter Ueda [6], Stefan James [1,2], Stephanie R. Reading [7], Paul J. Dluzniewski[7], Andrew W. Hamer[7], Tomas Jernberg [5], and Emil Hagström[1,2]



Eur Heart J 2021;42:243

What are the unmet needs in LDL-C lowering?

40,607 patients post myocardial infarction



Eur Heart J 2021;42:243

LDL-C: should we go lower after ACS ?

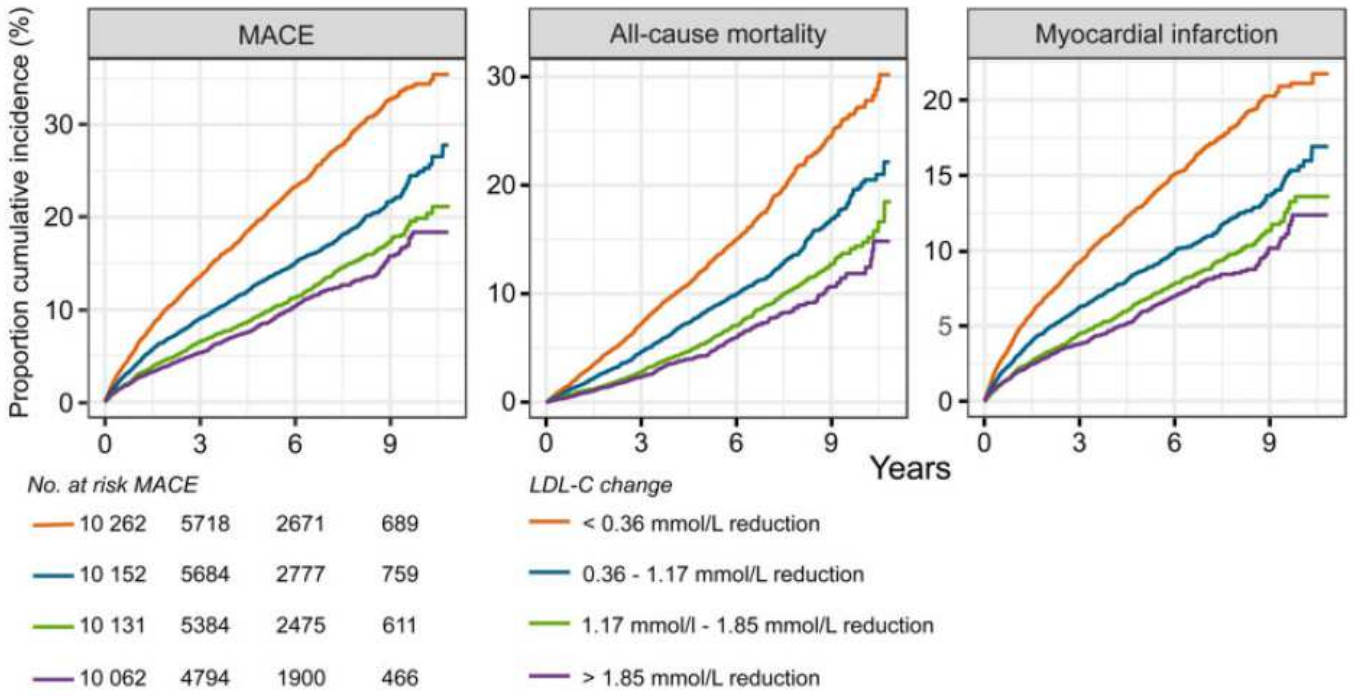
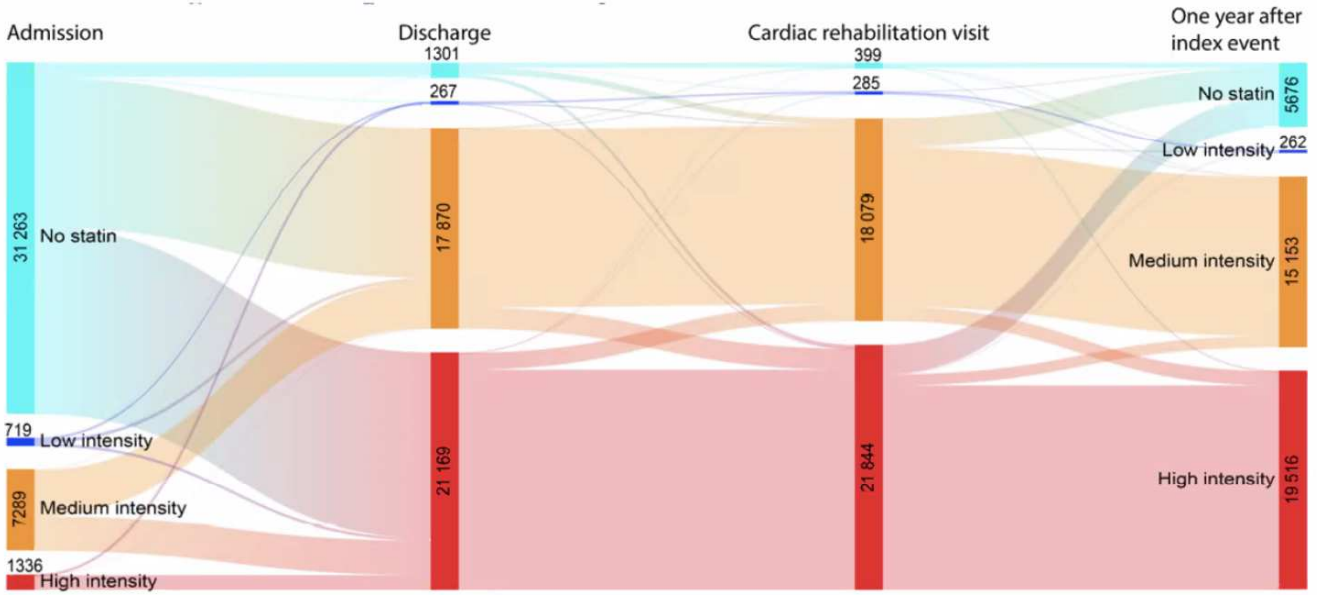


Figure 1 Kaplan–Meier curves of the cumulative incidence rates by quartile low-density lipoprotein cholesterol (LDL-C) change from index event to the cardiac rehabilitation visit. Outcomes are assessed after the cardiac rehabilitation visit. Numbers at risk shown for MACE. MACE, major adverse cardiovascular event is the composite outcome of cardiovascular mortality, myocardial infarction, and ischaemic stroke.

Eur Heart J 2021;42:243

Statin intensity on admission, at discharge, cardiac rehabilitation, and one year after index event among 40,607 pts **post-MI**



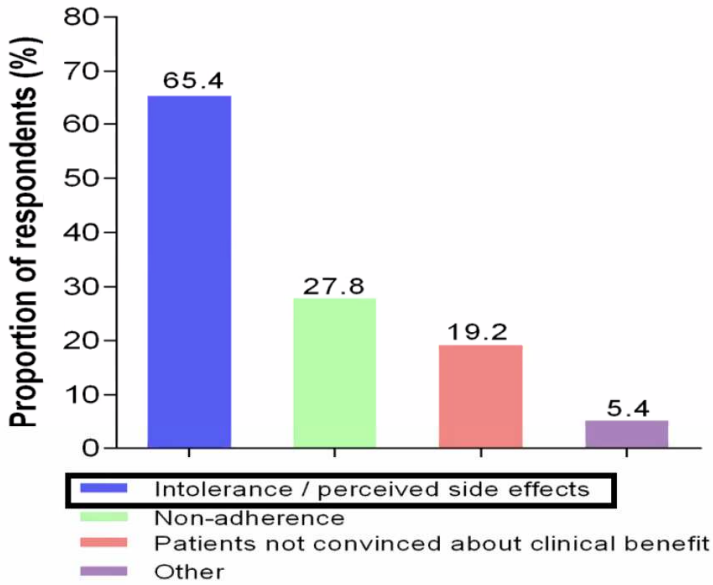
High-intensity statin

Only ≈ 50% of patients receive high-intensity therapy at discharge and after 1 year

Eur Heart J 2021;42:243

Why is statins not prescribe?

Survey by the ESC/EAS among 1,271 physicians



Reason for not prescribing a statin in patients with ASCVD

Eur J Preventive Cardiology 2021;22:59

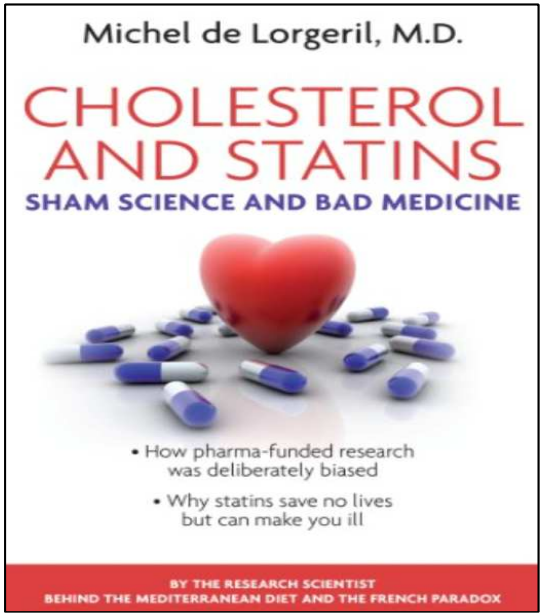
MAGAZINE D'AOÛT 2016
DE LA CAISSE MALADIE CSS

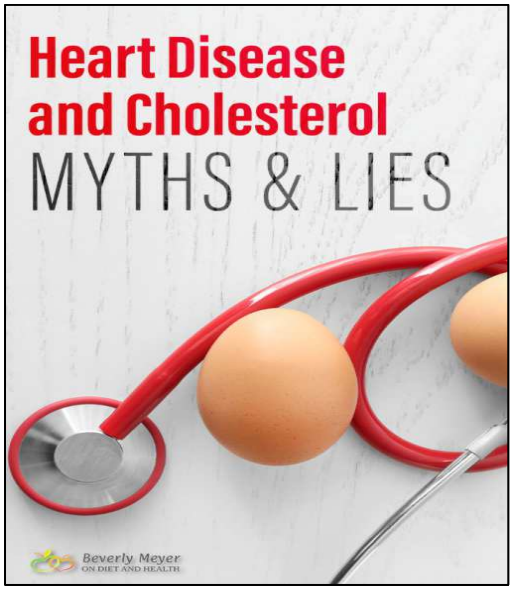
Et si le cholestérol n'était pas dangereux?

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-



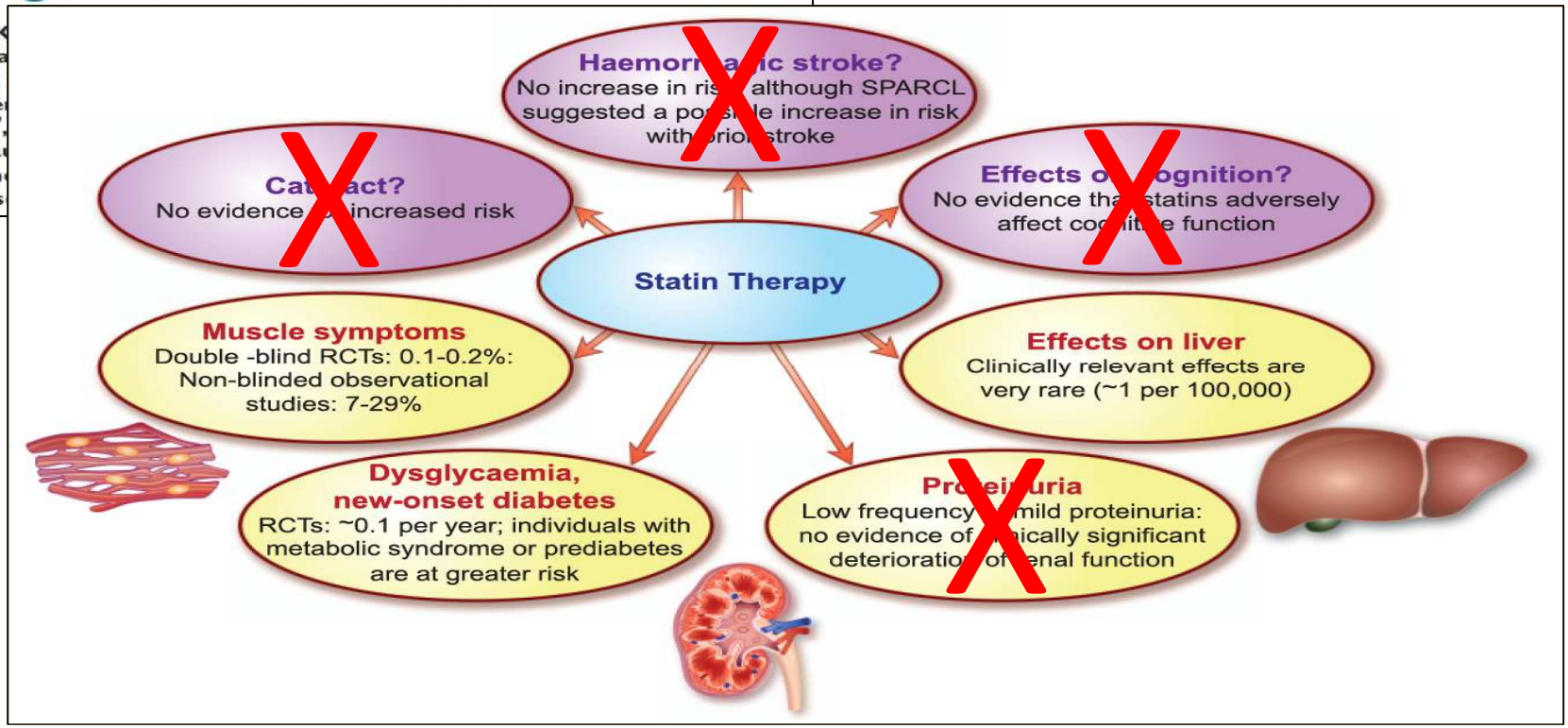


ESC European Society of Cardiology
European Heart Journal (2018) 0, 1–18
doi:10.1093/eurheartj/ehy182
REVIEW

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]*, K
Alberico L. Catapa
G. Kees Hovingh[9],
Lawrence A. Leite
Frederick J. Raal[19],
Erik S. Stroes[9], Pa
Baris Gencer[1], Jan
European Atheros



Eur Heart J 2018;39:2526

Perception vs evidence – The nosebo effect

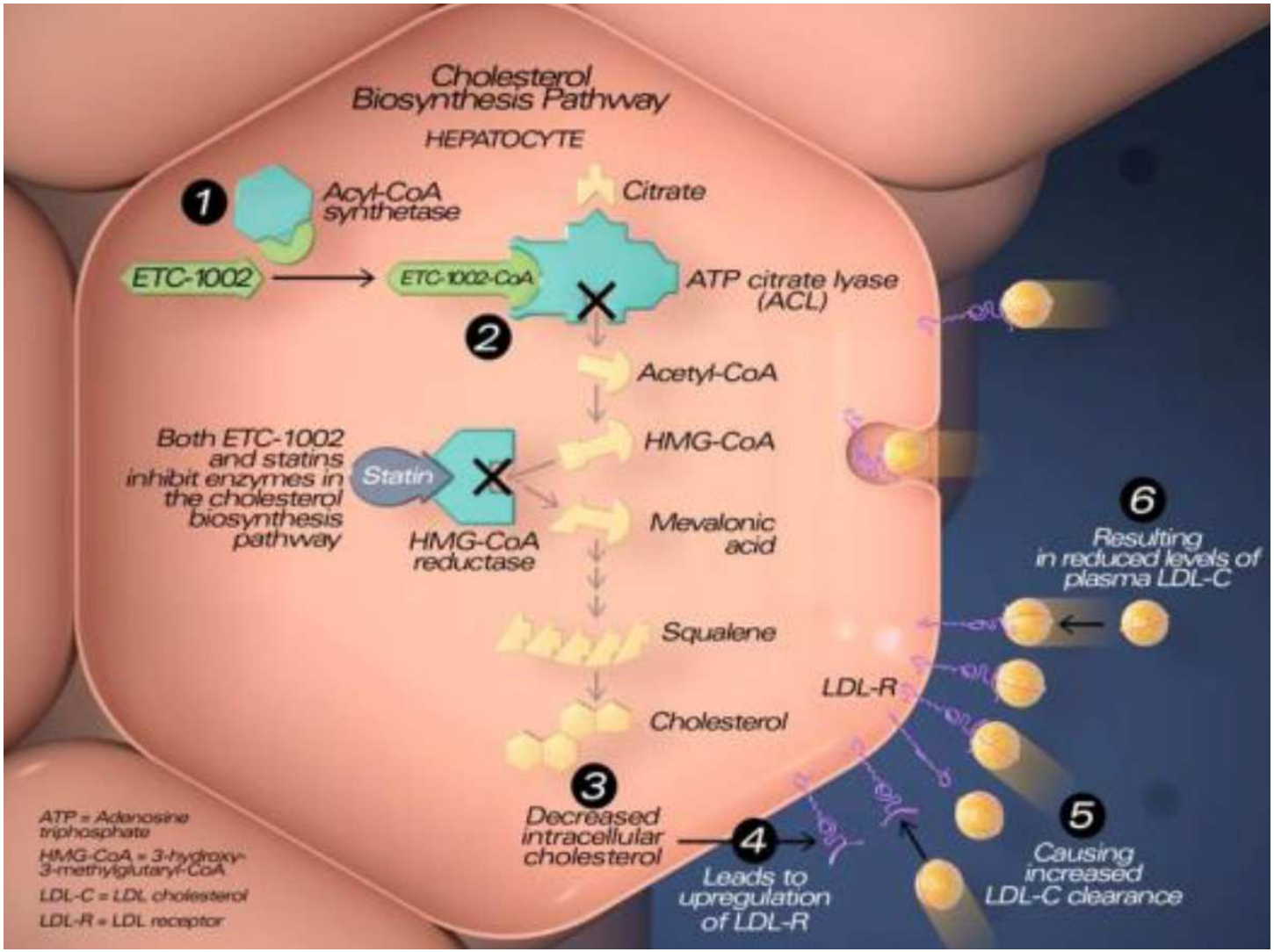
Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase

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

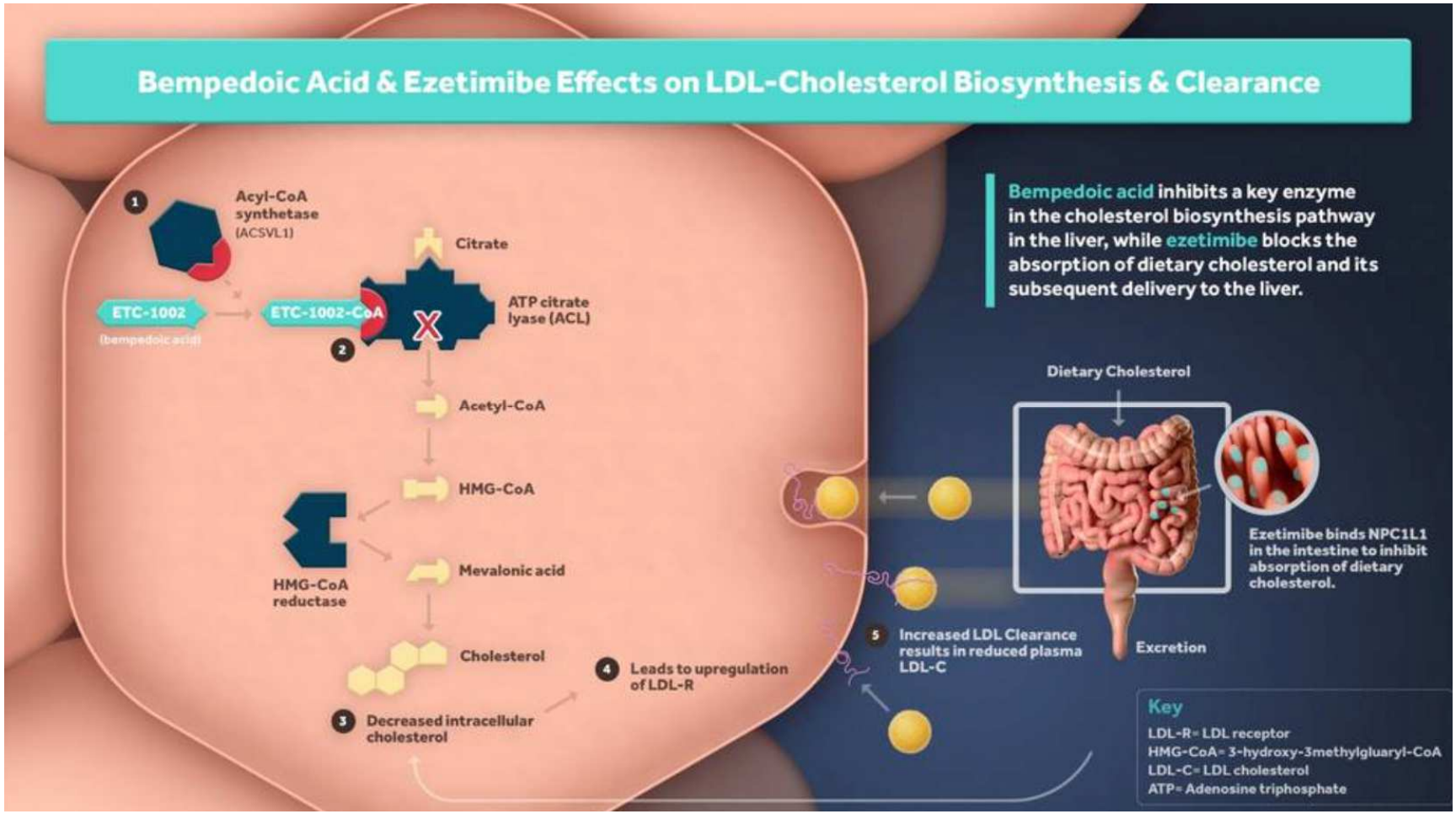
	Blinded randomised phase (ASCOT-LLA)		Non-blinded non-randomised phase	
	Placebo (n=5079)	Atorvastatin (n=5101)	Atorvastatin non-user (n=3490)	Atorvastatin user (n=6409)
Muscle related				
Patients (n)	283	298	124	161
AE rate (% per annum)	2·00%	2·03%	1·00%	1·26%
HR (95% CI)	1	1·03 (0·88–1·21)	1	1·41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

Lancet 2017;389:2473

Metabolism of Cholesterol Synthesis



Metabolism of Cholesterol Synthesis



Bempedoic acid to reduce LDL-C

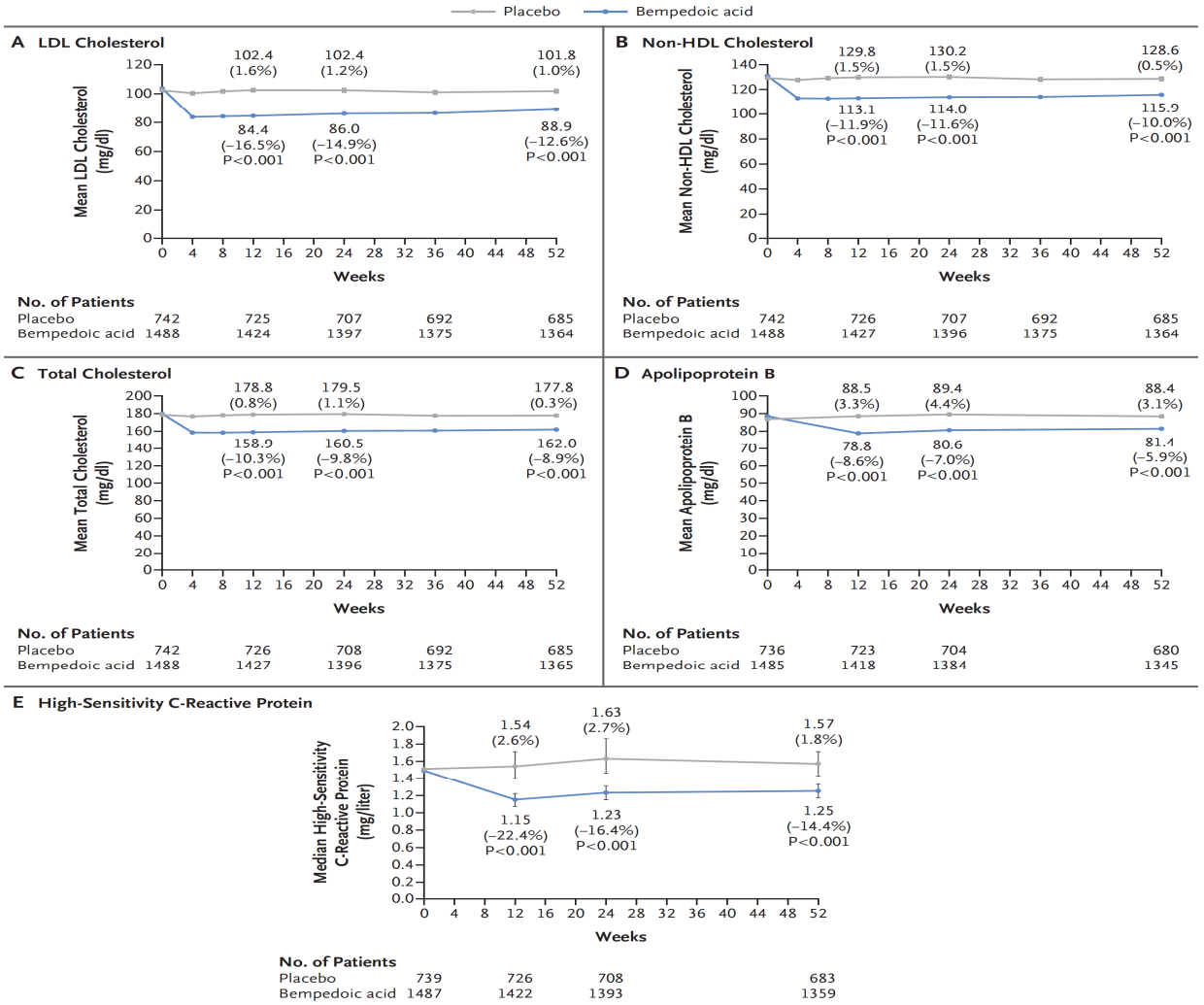
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., Harold E. Bays, M.D., Alberico L. Catapano, Ph.D., Narendra D. Lalwani, Ph.D., M.B.A., LeAnne T. Bloedon, M.S., R.D., Lulu R. Sterling, Ph.D., Paula L. Robinson, M.S., and Christie M. Ballantyne, M.D., for the CLEAR Harmony Trial*

New Engl J Med 2019;380:1022

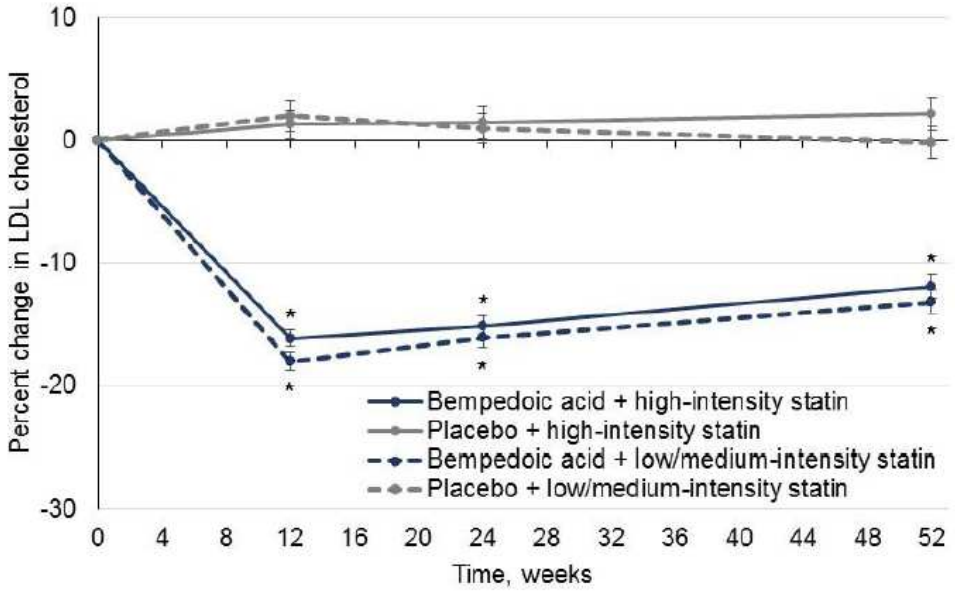


CLEAR-Harmony

Efficacy endpoint

Percent Change in LDL cholesterol versus Time by Statin Intensity

ITT population (on treatment analysis)



BA + high-intensity statin, n	752	706	692	678
Placebo + high-intensity statin, n	374	362	356	343
BA +low/med-intensity statin, n	736	718	705	686
Placebo + low/medium-intensity statin, n	368	363	351	342

- The LDL-C lowering effect of Bempedoic Acid is maintained regardless of statin intensity.
- Bempedoic acid is more effective at lowering LDL-C when combined with low/med intensity statins.

New Engl J Med 2019;380:1022

CLEAR-Harmony

Safety Endpoints (1)

Overview of Treatment-Emergent Adverse Events*

Variable	Placebo (n=742)	Bempedoic acid (n=1487)	Relative Risk (95% CI)†
Adverse events			
Any adverse event	584 (78.7)	1167 (78.5)	1.00 (0.95, 1.04)
Serious adverse event	104 (14.0)	216 (14.5)	1.04 (0.83, 1.29)
Leading to discontinuation of study drug	53 (7.1)	162 (10.9)	1.53 (1.13, 2.05)
Death (all cause)	2 (0.3)	13 (0.9)	3.24 (0.73, 14.34)
Adjudicated MACE	42 (5.7)	68 (4.6)	0.81 (0.56, 1.17)
Cardiovascular death	1 (0.1)	6 (0.4)	2.99 (0.36, 24.82)
Nonfatal myocardial infarction	13 (1.8)	19 (1.3)	0.73 (0.36, 1.47)
Nonfatal stroke	2 (0.3)	5 (0.3)	1.25 (0.24, 6.41)
Coronary revascularization	24 (3.2)	38 (2.6)	0.79 (0.48, 1.31)
Hospitalization for unstable angina	11 (1.5)	14 (0.9)	0.64 (0.29, 1.39)
Other MACE-related events			
Noncoronary arterial revascularization	6 (0.8)	4 (0.3)	0.33 (0.09, 1.18)
Hospitalization for heart failure	1 (0.1)	9 (0.6)	4.49 (0.57, 35.38)
Noncardiovascular death‡	1 (0.1)	2 (0.1)	1.00 (0.09, 10.99)
Non-treatment-emergent death§	0	5 (0.3)	NC

Data are number of patients (percentage) unless otherwise specified. *Includes events occurring from the first dose through 30 days after the last dose of study drug. †Relative risks and confidence intervals were calculated as a post hoc analysis. ‡Noncardiovascular deaths were due to septic shock secondary to cecal perforation and acute peritonitis for 1 patient in the placebo group, and 1 case each of liver metastases of unknown primary origin and multi-organ failure in the bempedoic acid group.§Treatment-emergent deaths occurred within 30 days of last study drug dose; deaths deemed not treatment

CI, confidence interval; MACE, major adverse cardiac events; NC, not calculated

New Engl J Med 2019;380:1022

CLEAR-Harmony

Safety Endpoints (2)

Overview of Treatment-Emergent Adverse Events of Special Interest*

Variable	Placebo (n=742)	Bempedoic acid (n=1487)	Relative Risk (95% CI)†
Adverse events of special interest			
Muscular disorders	75 (10.1)	195 (13.1)	1.30 (1.01, 1.67)
Leading to discontinuation of study drug	14 (1.9)	31 (2.1)	1.10 (0.59, 2.06)
Myalgia	45 (6.1)	89 (6.0)	0.99 (0.70, 1.40)
Muscle spasms	20 (2.7)	62 (4.2)	1.55 (0.94, 2.54)
Pain in extremity	16 (2.2)	50 (3.4)	1.56 (0.89, 2.72)
Muscular weakness	4 (0.5)	9 (0.6)	1.12 (0.35, 3.63)
New onset or worsening diabetes	40 (5.4)	49 (3.3)	0.61 (0.41, 0.92)
Gout	2 (0.3)	18 (1.2)	4.49 (1.04, 19.30)
Change from baseline in uric acid – mg/dl	–0.06 (0.87)	0.73 (1.11)	NC
Blood creatinine increased	3 (0.4)	12 (0.8)	2.00 (0.56, 7.05)
Glomerular filtration rate decreased	0	8 (0.5)	NC
Neurocognitive disorders	7 (0.9)	11 (0.7)	0.78 (0.31, 2.01)

Data are number of patients (percentage) unless otherwise specified. *Includes events occurring from the first dose through 30 days after the last dose of study drug. †Relative risks and confidence intervals were calculated as a post hoc analysis.
CI, confidence interval; eGFR, estimated glomerular filtration rate; NC, not calculated

New Engl J Med 2019;380:1022

CLEAR-Harmony

Conclusions

Efficacy

- Levels of LDL cholesterol significantly reduced compared with placebo, from baseline to week 52.
- Efficacy stable regardless type or intensity of background lipid-lowering therapy. An increased efficacy was observed with low/moderate intensity statins compared to high intensity statins.

Safety

- An acceptable safety profile, with no overall higher incidence of adverse effects than placebo.
- No increase in Myalgias compared to placebo[1].
- Modest elevations in uric acid levels, presumably due to competition renal transporter competition.

New Engl J Med 2019;380:1022

Bempedoic acid for statin intolerance ?

U.S. National Library of Medicine
ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site

Home > Search Results > Study Record Detail

Save this study

Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid (ETC-1002) or Placebo (CLEAR Outcomes)

ClinicalTrials.gov Identifier: NCT02993406

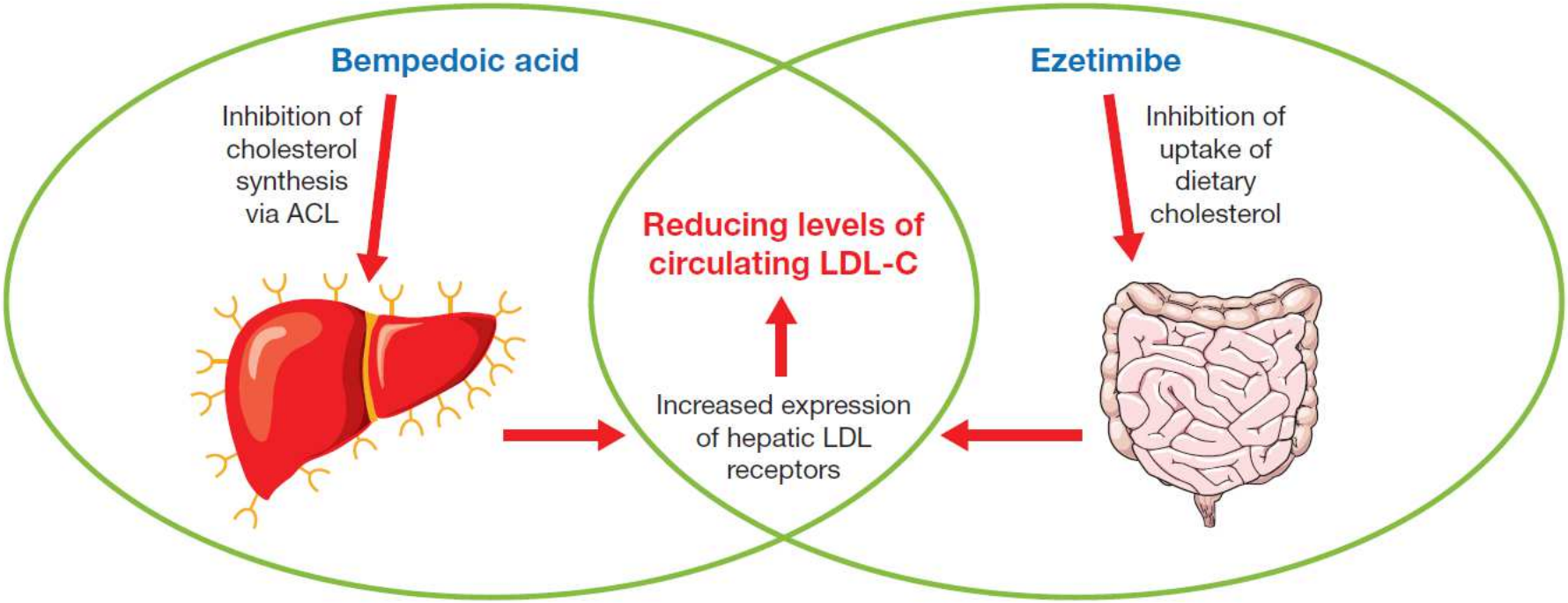
Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	12600 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Randomized, Double-blind, Placebo-controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant
Study Start Date :	December 2016
Estimated Primary Completion Date :	December 2021
Estimated Study Completion Date :	March 2022

Bempedoic Acid and Ezetimibe FDC:
Complementary Mechanisms of Cholesterol Synthesis Inhibition

Bempedoic acid and ezetimibe FDC combines the complementary mechanisms of cholesterol synthesis inhibition via ACL in the liver, with inhibition of cholesterol absorption in the intestines



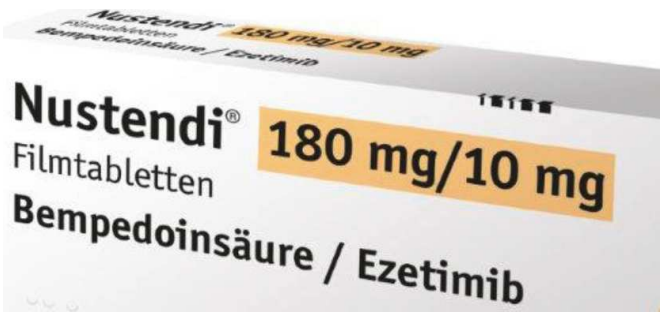
Bempedoic acid to reduce LDL-C

8.11 Future perspectives

8.11.1 New approaches to reduce low-density lipoprotein cholesterol

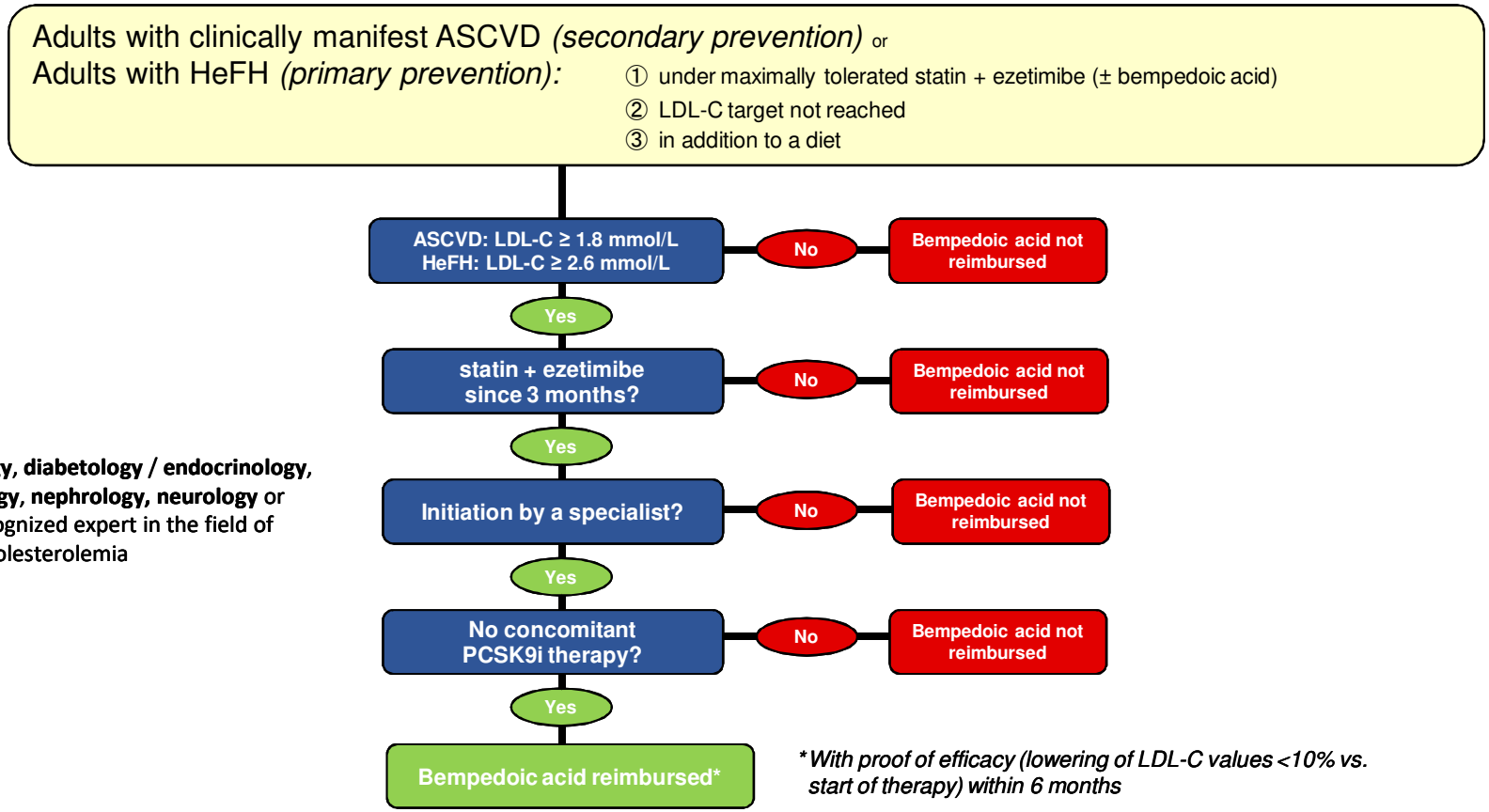
An alternative approach targeting PCSK9 consists of RNA interference. In a phase I and a phase II trial, the small interfering RNA (siRNA) molecule inclisiran—which inhibits the synthesis of PCSK9—reduced LDL-C by up to 50% and the reduction was dose-dependent. Reductions in PCSK9 and LDL-C levels were maintained for ≤6 months.[338,339] No specific serious adverse events were observed. HPS4/TIMI65/ORION4, with a planned mean duration of 5 years, is currently comparing inclisiran vs. placebo among 15 000 patients with a prior MI or stroke.

Bempedoic acid is a novel, first-in-class, oral small molecule that inhibits cholesterol synthesis by inhibiting the action of ATP citrate lyase, a cytosolic enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[340] So far, it has been tested in diabetic patients, and patients with or without statin 'intolerance'. In monotherapy, bempedoic acid reduces LDL-C levels by ~30% and by about 50% in combination with ezetimibe. Bempedoic acid is currently being tested in phase III trials and some trials have been completed.[341,342]



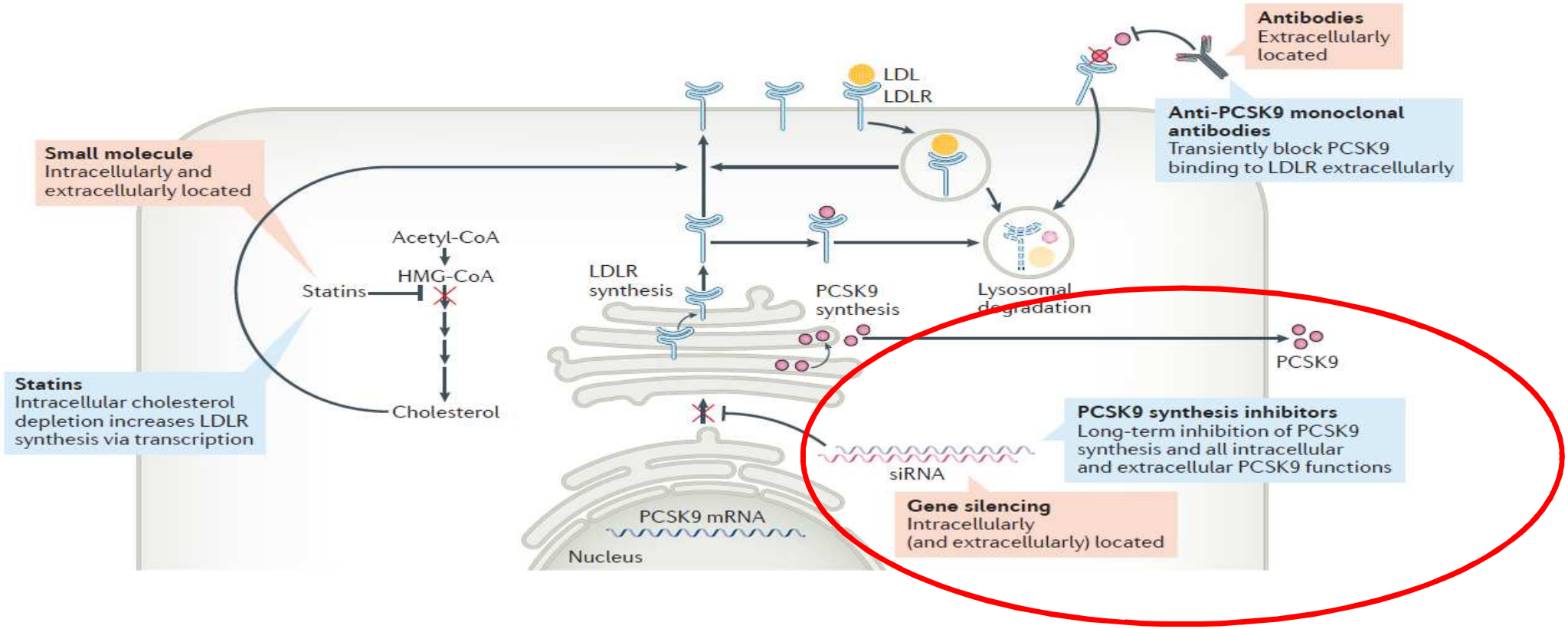
Eur Heart J 2020;41:111

NILEMDO® (bempedoic acid) **and NUSTENDI®** (bempedoic acid + ezetimibe)
Limites au remboursement



ASCVD: atherosclerotic cardiovascular disease; HeFH: heterozygote familial Hypercholesterolemia

Approaches to reduce LDL-C levels



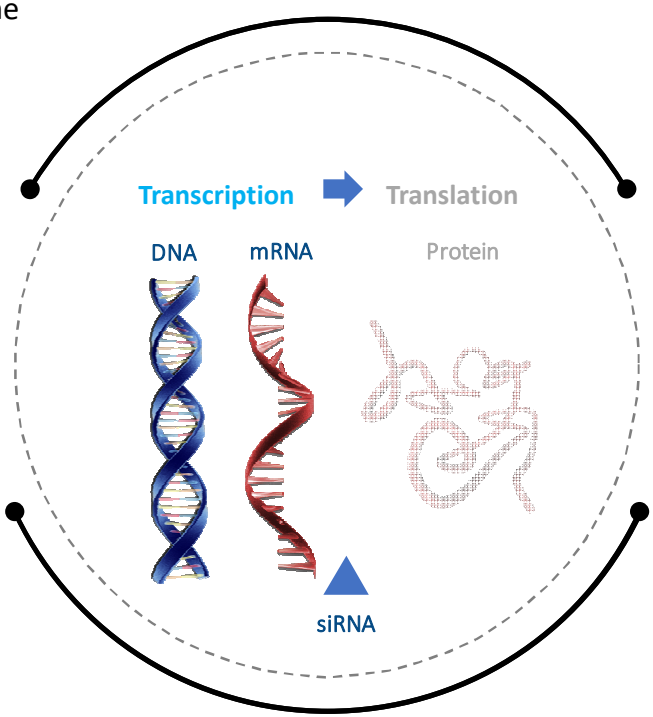
Nature Rev Cardiol 2018;15:261

Gene-Protein Synthesis

Non-coding RNAs

Only **~2%** of the human genome encodes proteins while a significant portion codes for **non-coding RNAs** (ncRNAs)[1]

Small interfering RNAs (siRNAs) are short double-stranded ncRNAs that function in gene silencing[2,3]



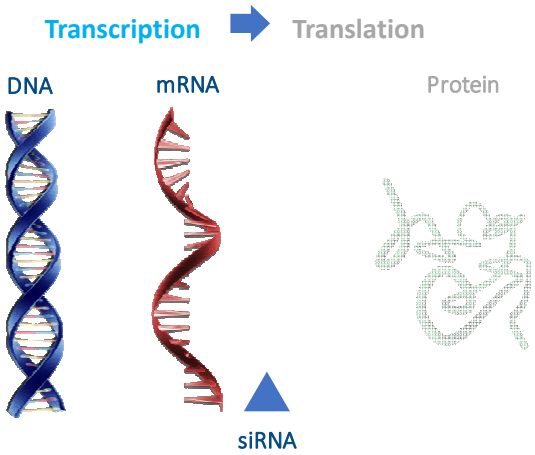
ncRNAs are involved in **gene regulation**, RNA maturation and protein synthesis[1]

siRNAs **prevent protein synthesis** by degrading unique target mRNA through a natural mechanism called RNA interference[2,3]

[1]*Vascul Pharmacol.* 2019;114:64 [2]*Mol Ther Nucleic Acids.* 2015;4:e252 [3]*Annu Rev Biophys.* 2013;42:217

RNA Therapeutics

Synthetic small RNA



In 2006, Andrew Fire and Craig Mello were awarded the Nobel Prize for Physiology or Medicine for their discovery of RNAi, initiating an era of RNA therapeutics (highly specific drugs)[1]

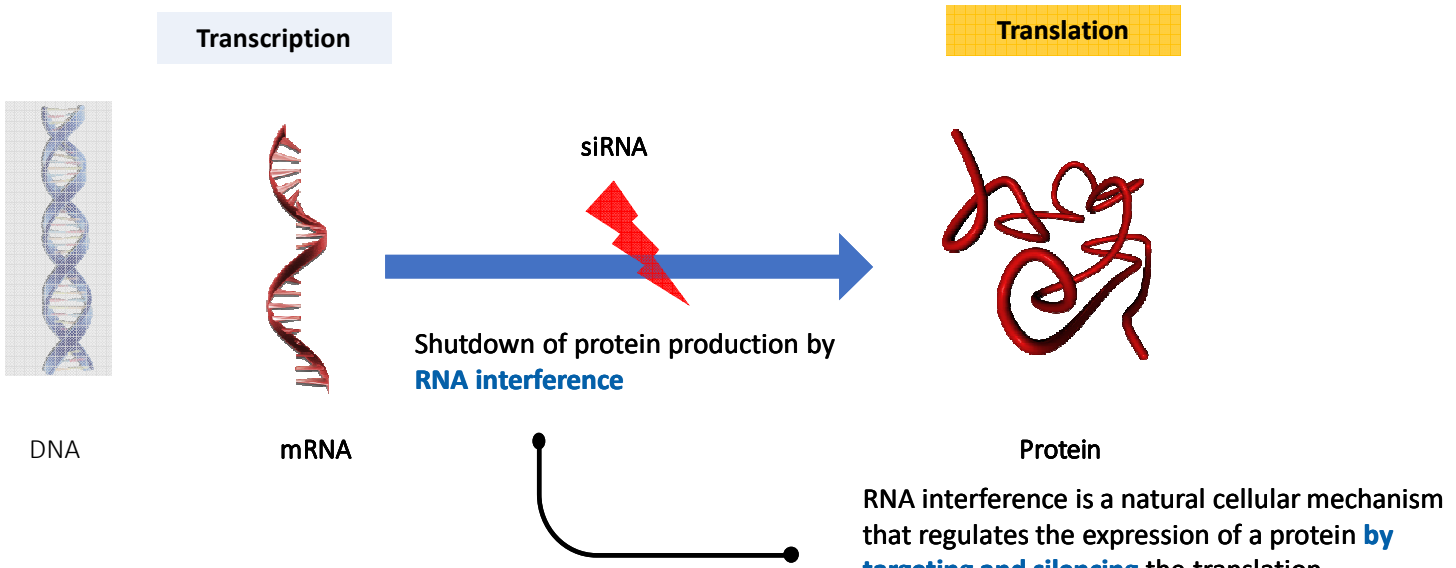
RNAi therapeutics harness the natural biologic pathway of RNAi to regulate expression of specific genes[2]

Advances in RNA therapeutics focus on gene silencing using synthetic short ncRNA, including siRNA, to regulate and/or silence target genes[2,3]

Synthetic siRNA targets a unique mRNA nucleotide sequence and can theoretically target any gene of interest[2]

[1]The Nobel Prize in Physiology or Medicine 2006. NobelPrize.org. https://www.nobelprize.org/prizes/medicine/2006/summary
[2]*Mol Ther Nucleic Acids.* 2015;4:e252
[3]*Cell Metab.* 2018;27:714

RNA interference enables a cell to specifically shut down protein production



RNA interference is a natural cellular mechanism that regulates the expression of a protein **by targeting and silencing** the translation corresponding **mRNA**[1,2]

[1]*Mol Ther Nucleic Acids.* 2015;4:e252 [2]*Annu Rev Biophys.* 2013;42:217

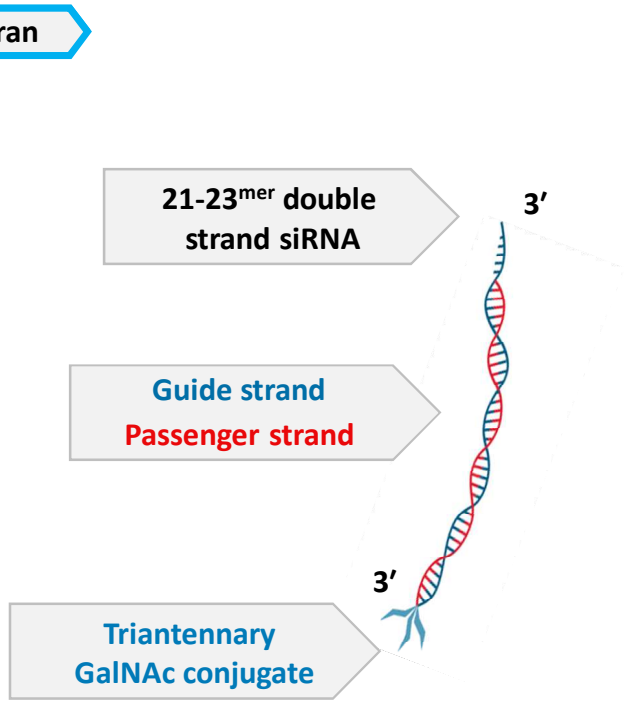
What is inclisiran ?

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]

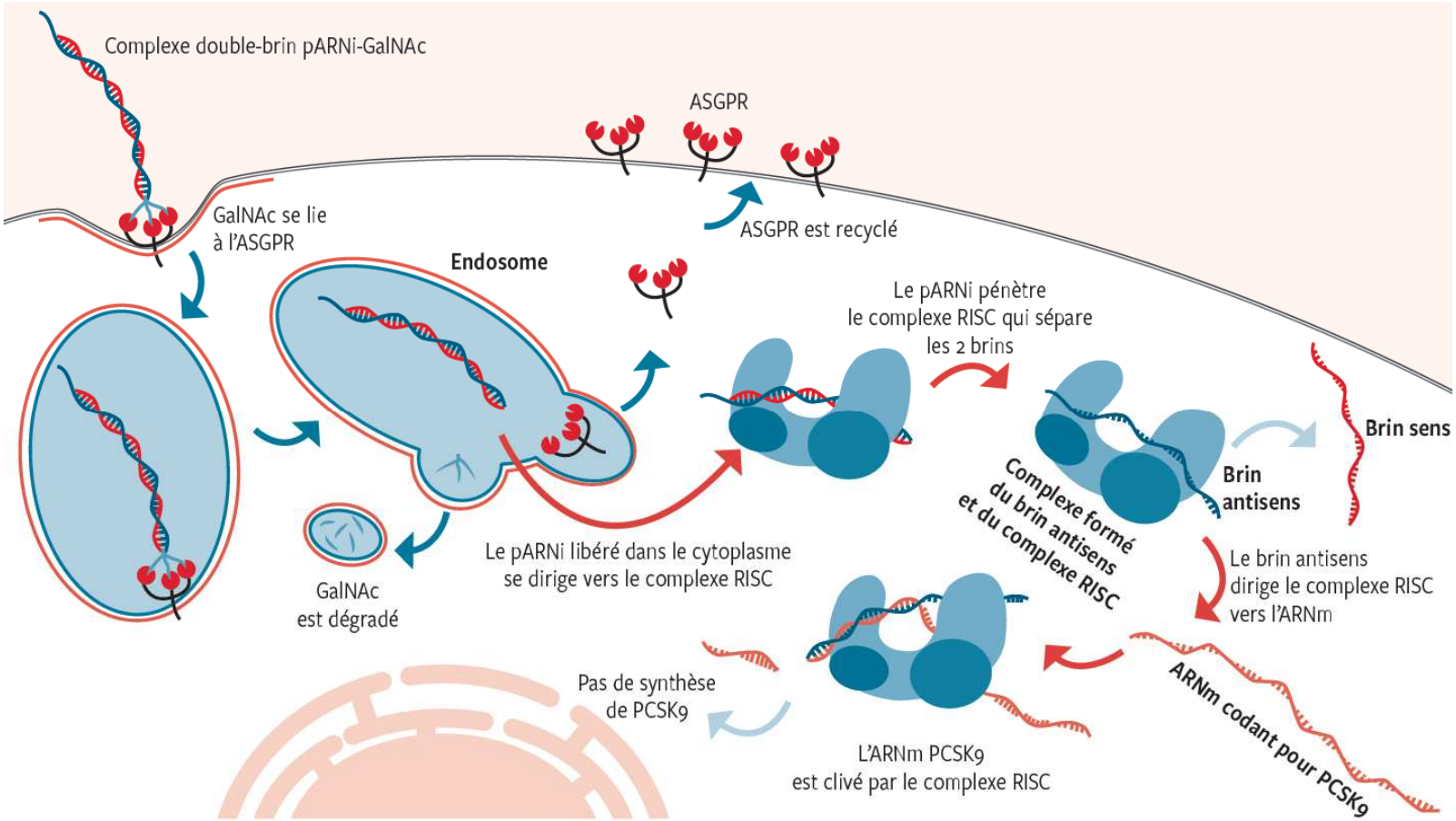
- 2′-fluoro and 2′-O-methyl modifications to **increase compound stability**
- Backbone phosphodiester linkages modified with phosphorothioates **to protect from degradation** by liver exonucleases
- Triantennary GalNAc conjugation for **targeted hepatic delivery**



[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;740:1039

Inclisiran treatment

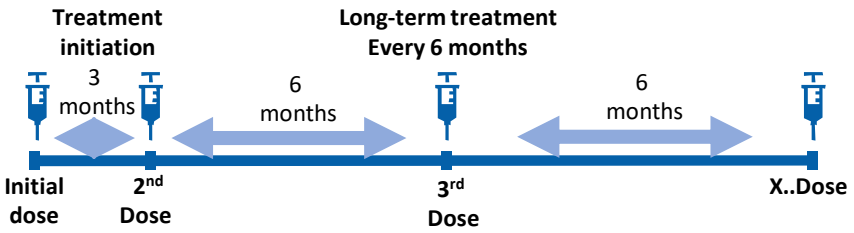
Dose & administration

Injection[1,2]

1.5 mL solution per syringe

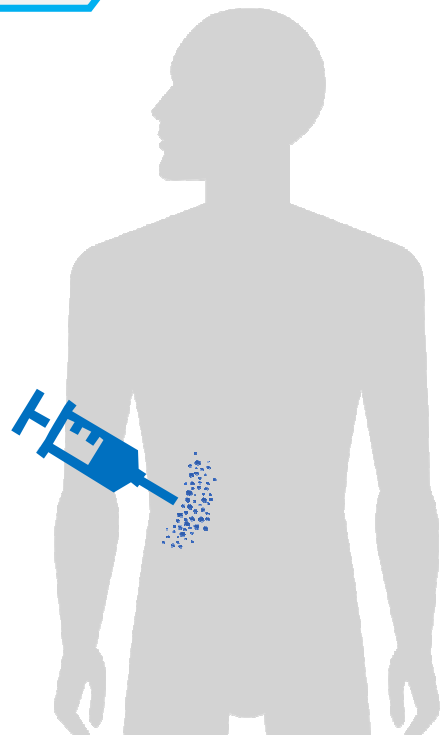
- 300 mg inclisiran sodium*
- Water as the diluent
- Sodium hydroxide and phosphoric acid (pH 7)
- Stored at room temperature

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

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;740:1039

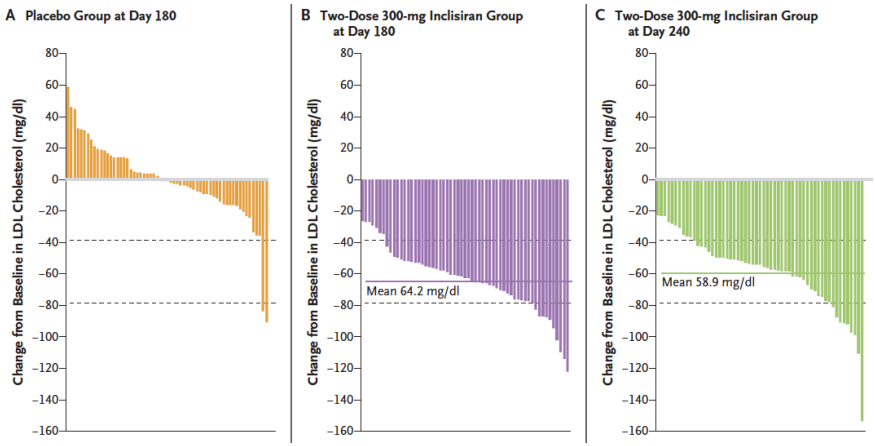
Lowering PCSK9 with siPCSK9

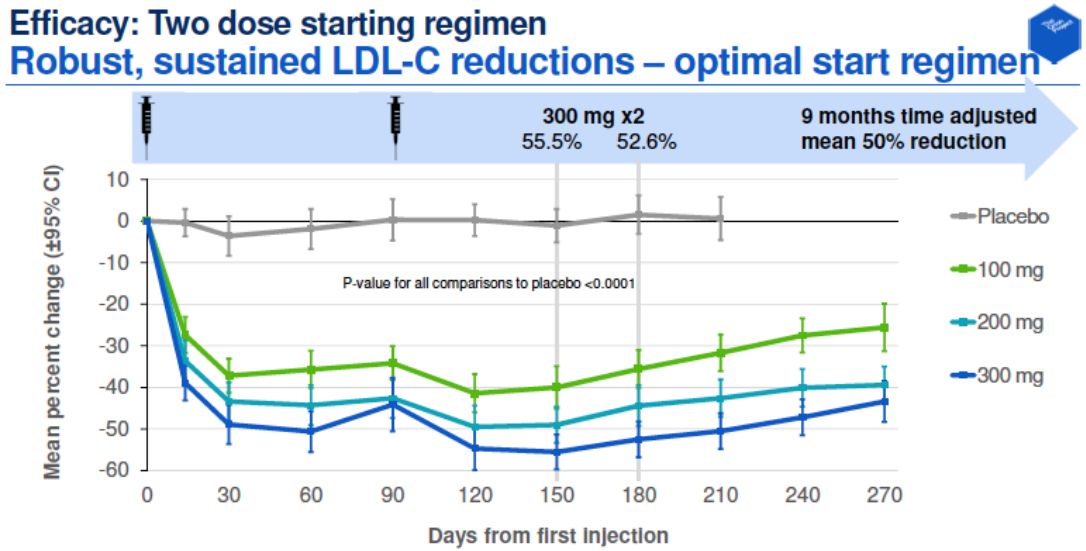
The NEW ENGLAND JOURNAL of MEDICINE

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.



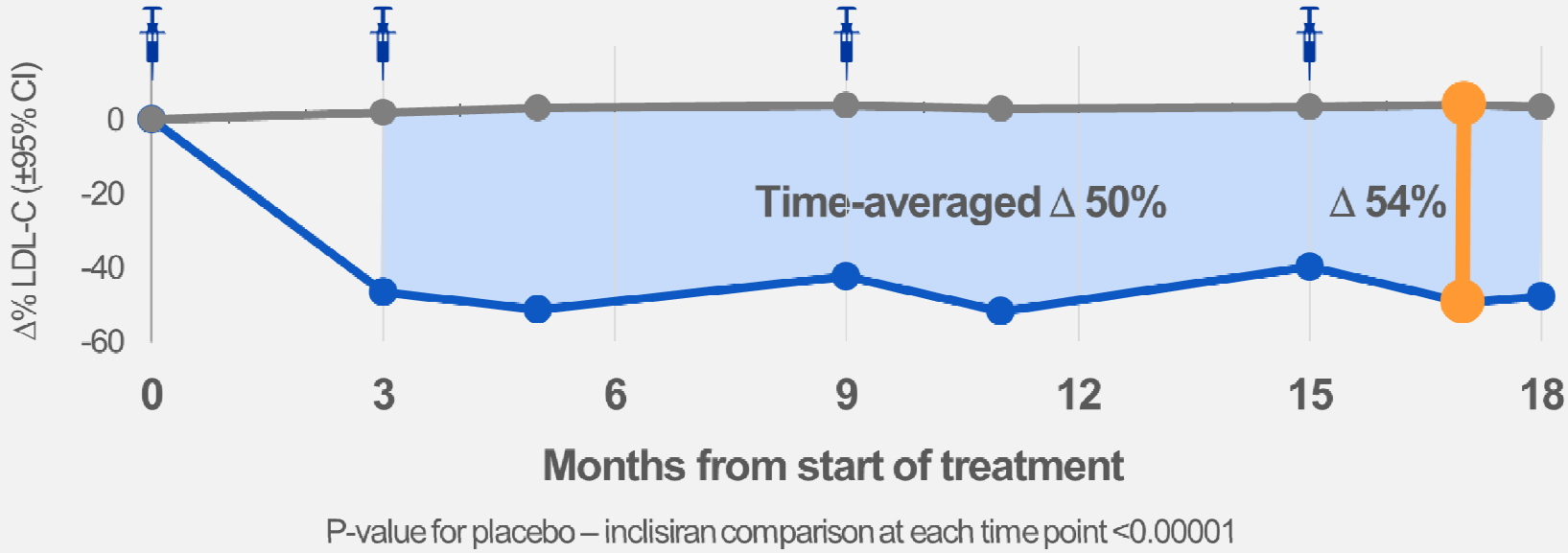


New Engl J Med 2017;376:1430

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

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

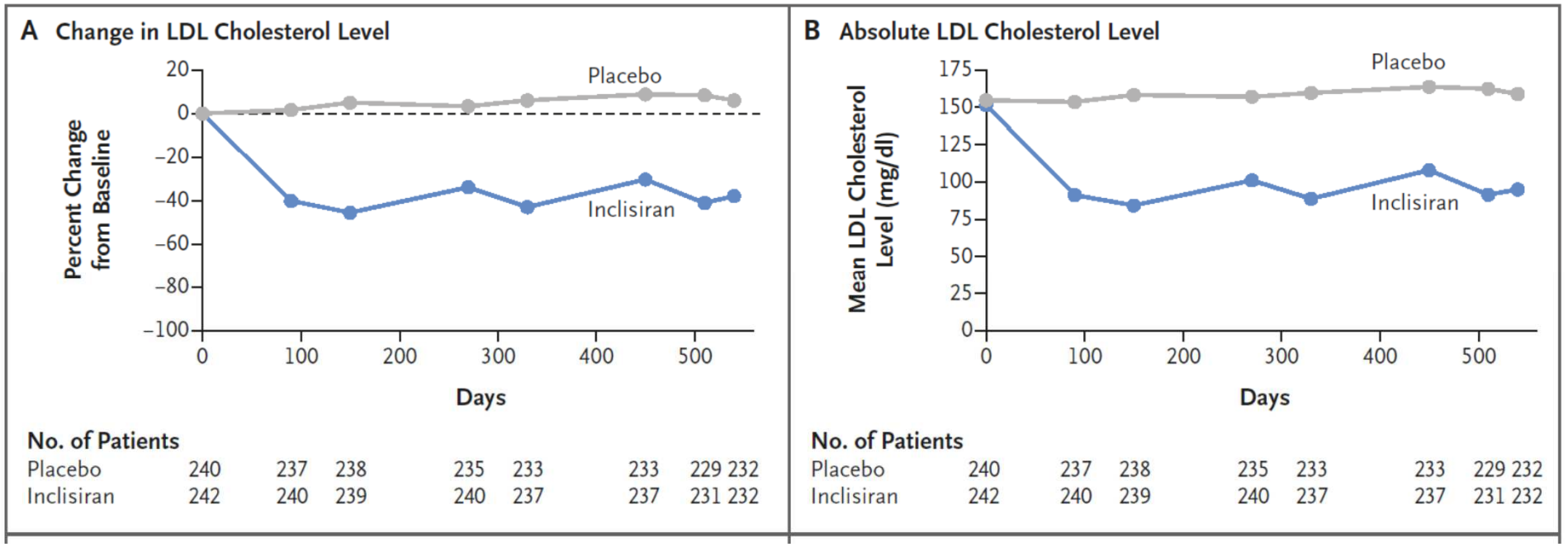


1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

New Engl J Med 2020;382:1507

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

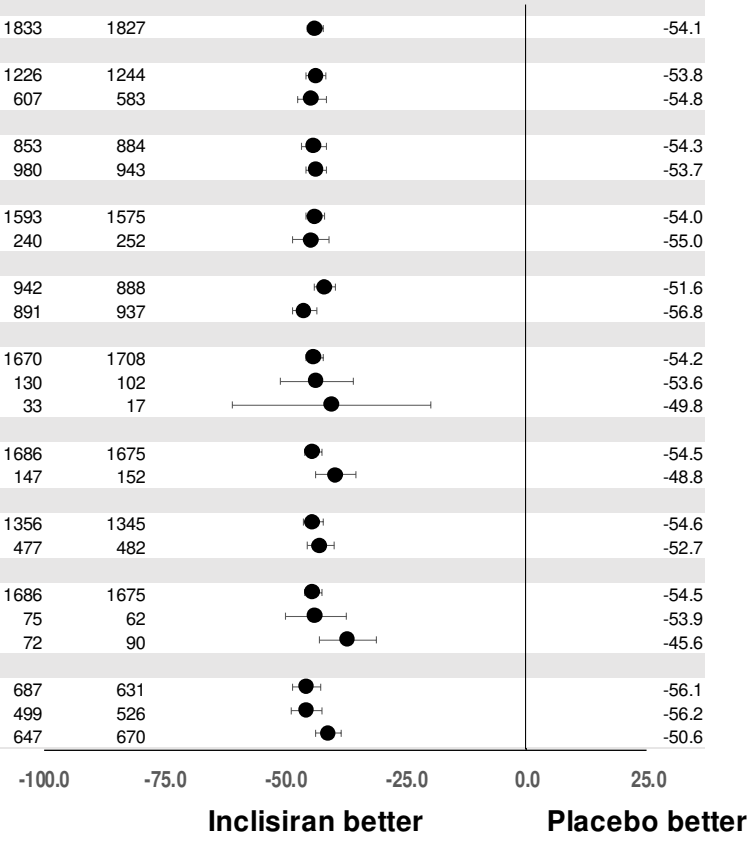


New Engl J Med 2020;382:1507

ORION Phase III pooled analysis: Efficacy

Robust ↓LDL-C across pre-specified sub-populations

Subgroup	Inclisiran N	Placebo N	LS Mean Percent Difference in LDL-C
Overall			
Overall	1833	1827	-54.1
Sex			
Male	1226	1244	-53.8
Female	607	583	-54.8
Age <65 yr or ≥65 yr			
<65 yr	853	884	-54.3
≥65 yr	980	943	-53.7
Age <75 yr or ≥75 yr			
<75 yr	1593	1575	-54.0
≥75 yr	240	252	-55.0
Body mass index			
≤29.7	942	888	-51.6
>29.7	891	937	-56.8
Race			
White	1670	1708	-54.2
Black	130	102	-53.6
Other	33	17	-49.8
Baseline statin treatment			
On statin	1686	1675	-54.5
Not on statin	147	152	-48.8
Intensity of statin treatment			
High intensity statin	1356	1345	-54.6
Not on high intensity statin	477	482	-52.7
Lipid management treatment (LMT)			
Any statin	1686	1675	-54.5
Other LMT but no statin	75	62	-53.9
No LMT	72	90	-45.6
Metabolic disease			
Diabetes	687	631	-56.1
Metabolic syndrome	499	526	-56.2
Neither	647	670	-50.6



New Engl J Med 2020;382:1507

ORION-11: Safety and tolerability

Adverse event profile similar to placebo

Treatment Emergent Adverse Event (TEAE)	Placebo		Inclisiran	
Safety population[1] – AEs in ≥5% patients	N = 807		N = 810	
Patients with at least one TEAE	**655**	**(82%)**	**671**	**(83%)**
Diabetes mellitus adverse events	94	(12%)	88	(11%)
Nasopharyngitis	90	(11%)	91	(11%)
Hypertension	54	(7%)	53	(7%)
Upper respiratory tract infection	49	(6%)	52	(6%)
Arthralgia	32	(4%)	47	(6%)
Osteoarthritis	40	(5%)	32	(4%)

1. Safety population includes all patients who received at least 1 dose of study medication
2. Other TEAEs reported with lower frequencies than 5% in any group had no clinically meaningful differences

New Engl J Med 2020;382:1507

ORION-11: Safety and tolerability

Injection site AEs localized, mostly mild and transient

Injection site TEAEs	Placebo		Inclisiran		Difference
Safety population[1]	N = 807		N = 810		
Protocol-defined skin event	**4**	**(0.50%)**	**38**	**(4.69%)**	**4.19%**
(Reaction, erythema, rash, pruritus, hypersensitivity)					
Mild	3	(0.37%)	23	(2.84%)	2.46%
Moderate	1	(0.13%)	15	(1.85%)	1.73%
Severe	0	(0.0%)	0	(0.0%)	
Persistent	0	(0.0%)	0	(0.0%)	

1. Safety population includes all patients who received at least 1 dose of study medication

New Engl J Med 2020;382:1507

ORION-11: Safety and tolerability

No evidence of liver, kidney, muscle or platelet toxicity

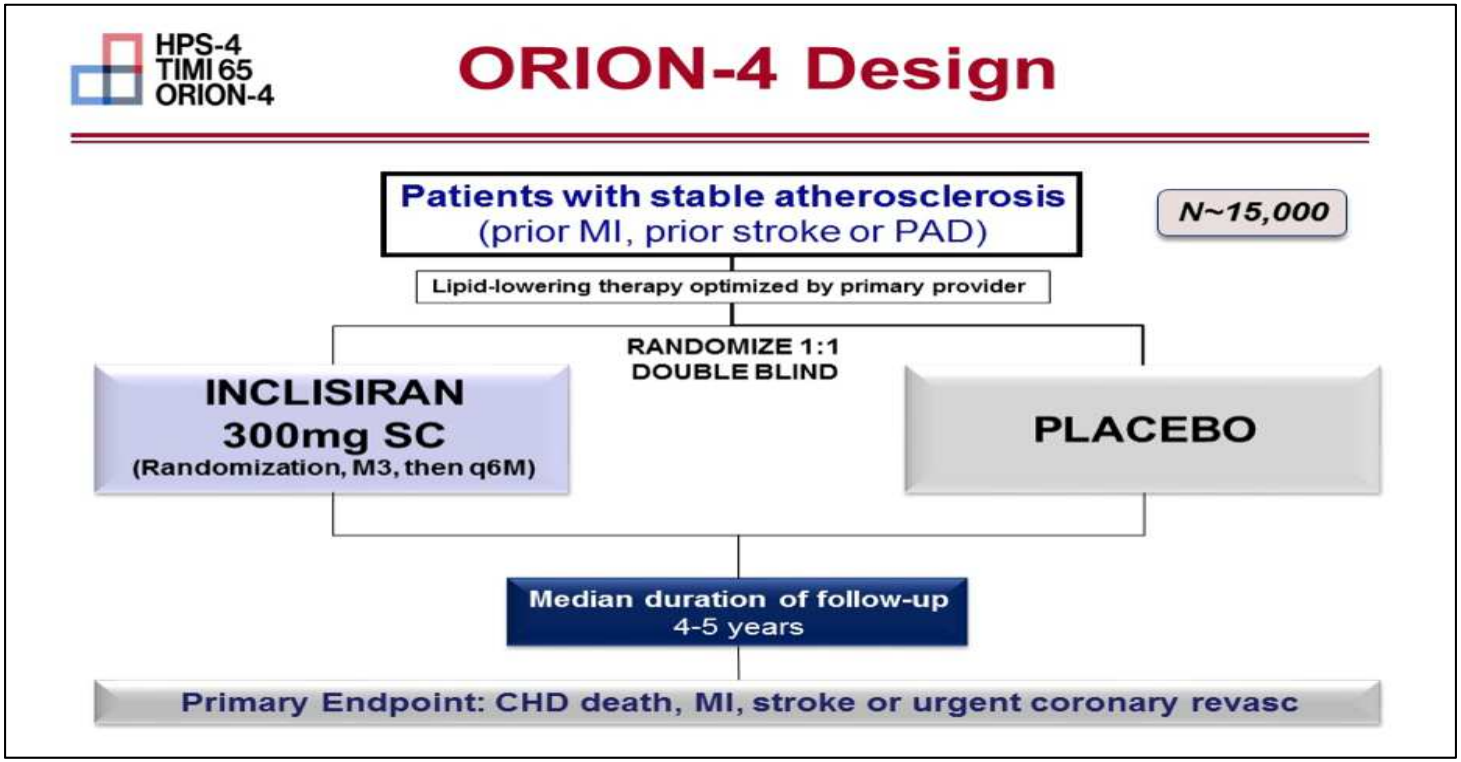
Laboratory Tests		Placebo		Inclisiran	
Safety population[1,2]		N = 804		N = 811	
Liver function	ALT >3x ULN	4	(0.5%)	4	(0.5%)
	AST >3x ULN	4	(0.5%)	2	(0.2%)
	ALP >2x ULN	2	(0.2%)	1	(0.1%)
	Bilirubin >2x ULN[3]	8	(1.0%)	6	(0.7%)
Kidney function	Creatinine >2 mg/dL	11	(1.4%)	5	(0.6%)
Muscle	CK >5x ULN	9	(1.1%)	10	(1.2%)
Hematology	Platelet count <75x10^9/L	1	(0.1%)	0	(0.0%)

1. Safety population includes all patients who received at least 1 dose of study medication
2. Patients may be counted in more than one category
3. No cases met Hy's Law

New Engl J Med 2020;382:1507

Opportunities and challenges for the future

Efficacy of different approaches to lipid lowering



Inclisiran clinical studies

ORION development program

2 premières injections suisses début mai 2021

Étude	Phase clinique	Patients (N)	Population étudiée	Durée de suivi	Critère de jugement	Référence ClinicalTrials.gov
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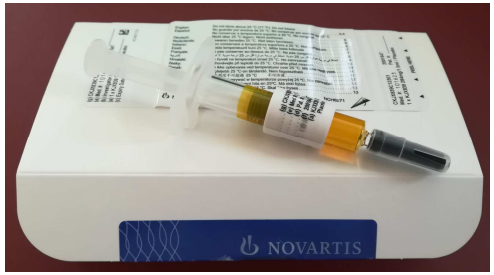


Inclisiran / Leqvio®

Indications cliniques / SwissMedic

LEQVIO

Composition

Principes actifs

Inclisiran (sous forme d'inclisiran sodique).

Indications/Possibilités d'emploi

Hypercholestérolémie et dyslipidémie mixte

Leqvio est indiqué chez l'adulte présentant une hypercholestérolémie [incluant hypercholestérolémie familiale hétérozygote] ou une dyslipidémie mixte, en complément d'un régime alimentaire:

- en association avec une dose de statine maximale tolérée avec ou sans autres traitements hypolipémiants chez les patients ayant besoin d'une diminution supplémentaire du cholestérol des lipoprotéines de basse densité (LDL-c) ou
- seul ou en association avec d'autres traitements hypolipémiants chez les patients intolérants aux statines ou présentant une contre-indication aux satines.

L'effet de Leqvio sur la morbidité et la mortalité cardiovasculaires n'a pas encore été déterminé à ce jour.

Inclisiran / Leqvio®

Indications cliniques

Posologie/Mode d'emploi

Posologie usuelle

Hypercholestérolémie et dyslipidémie mixte

La dose recommandée de Leqvio est de 284 mg sous forme d'une injection sous-cutanée unique en début de traitement, puis après 3 mois et ensuite tous les 6 mois.

En relais d'un traitement par anticorps monoclonal inhibiteur de PCSK9

Leqvio peut être administré immédiatement après le dernier traitement par un anticorps monoclonal inhibiteur de PCSK9. Afin de maintenir la diminution du LDL-c, il est recommandé d'administrer Leqvio dans les 2 semaines suivant le dernier traitement par un anticorps monoclonal inhibiteur de PCSK9.

Inclisiran / Leqvio®

Indications cliniques

Patients présentant des troubles de la fonction hépatique

Aucun ajustement posologique n'est nécessaire chez les patients présentant une insuffisance hépatique légère à modérée.

Patients présentant des troubles de la fonction rénale

Aucun ajustement posologique n'est nécessaire chez les patients présentant une insuffisance rénale légère, modérée ou sévère, ni chez les patients présentant une insuffisance rénale terminale.

Interactions

L'inclisiran n'est pas un substrat des transporteurs de médicaments usuels et, bien qu'aucune étude *in vitro* n'ait été réalisée, il ne devrait pas être un substrat du cytochrome P450. L'inclisiran n'est pas un inhibiteur ni un inducteur des enzymes cytochrome P450 (incluant CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 ou CYP3A4/5) ni des transporteurs de médicaments usuels (incluant OAT1, OAT3, OCT1, OCT2, OCT3, OATP1B1, OATP1B3 ou la P-gp). Leqvio ne devrait donc pas entraîner d'interactions cliniquement significatives avec d'autres médicaments.
Sur la base des données disponibles limitées, aucune interaction cliniquement significative avec l'atorvastatine, la rosuvastatine ou d'autres statines n'est attendue.

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

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

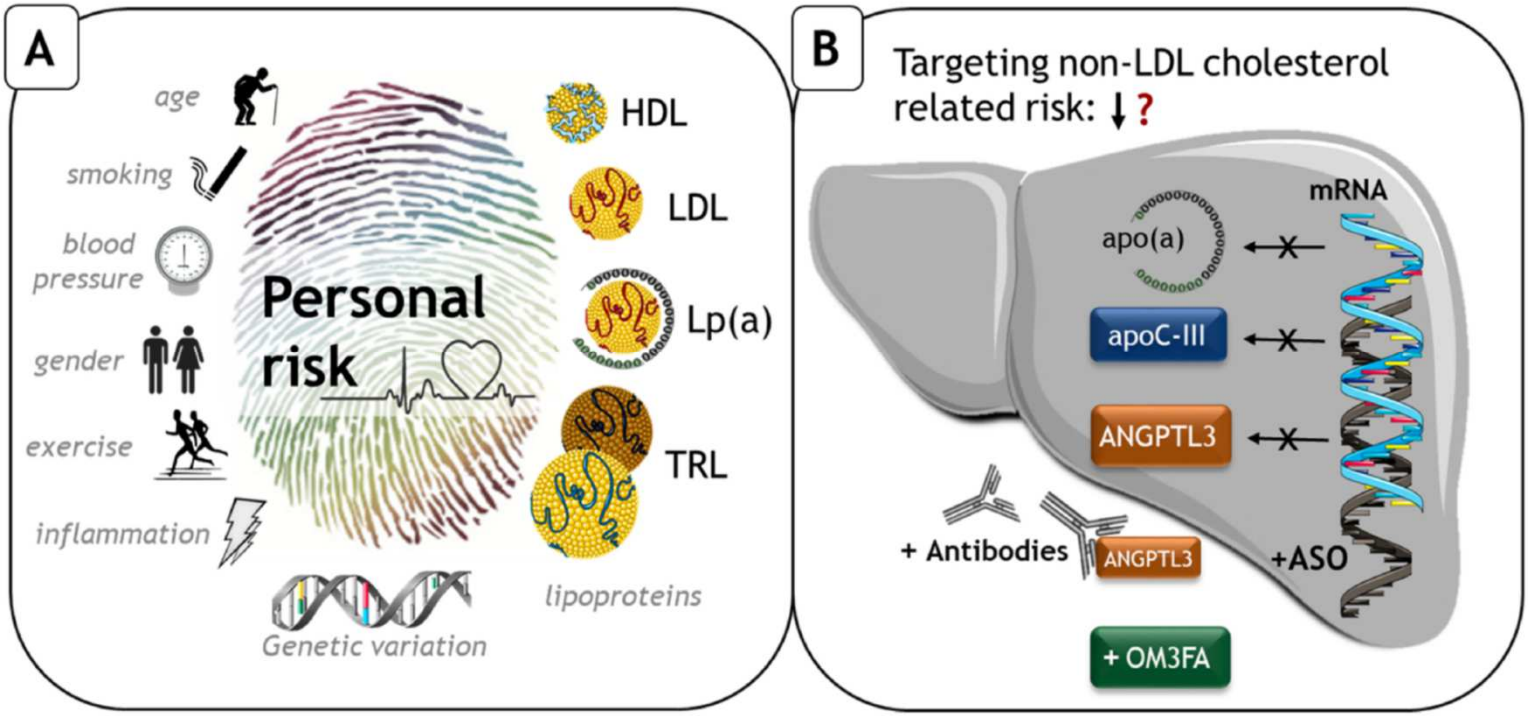
Pr FRANÇOIS MACH et Pr OLIVIER MULLER

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]

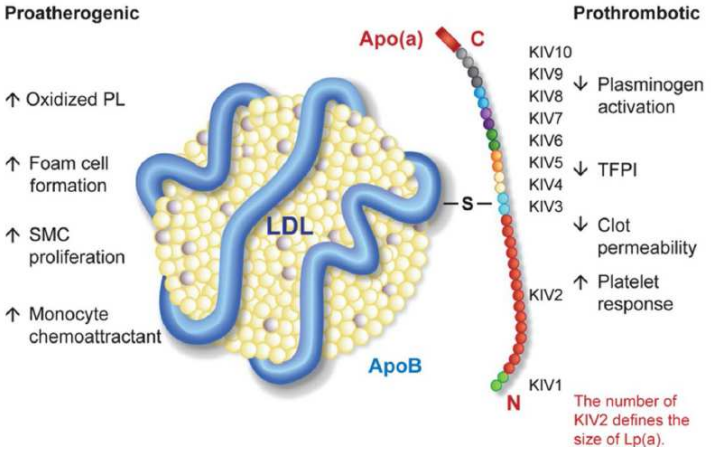
Rev Med Suisse 26 mai 2021;740:1039

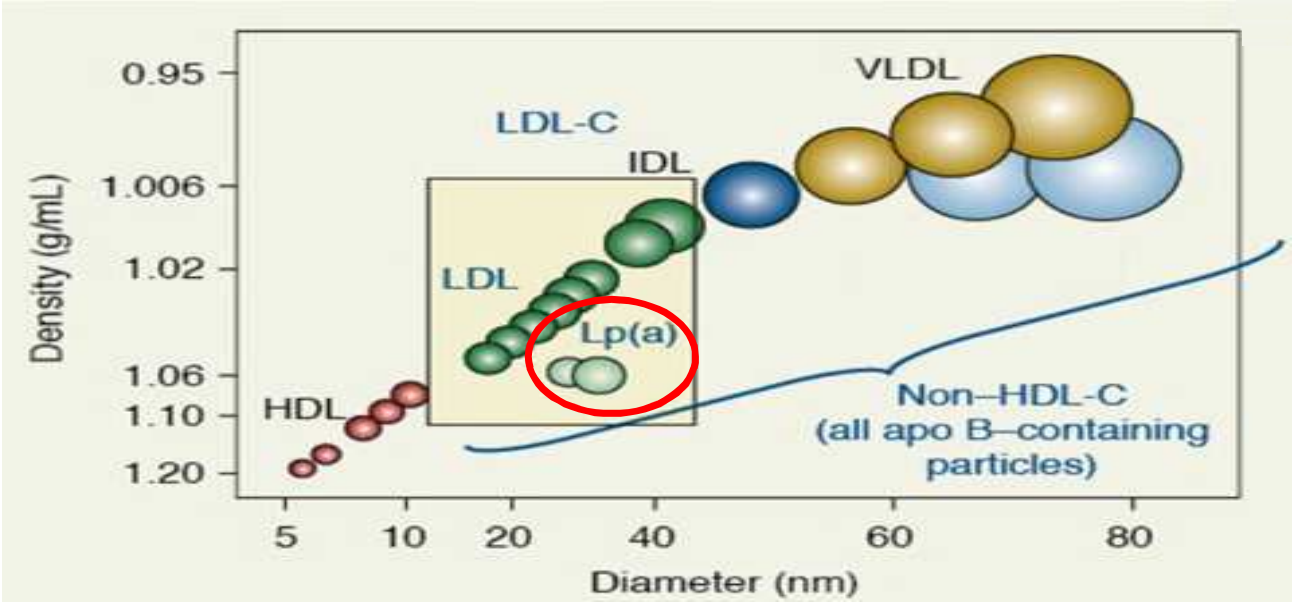
Novel lipid lowering drugs: PCSK9 and beyond



Clin Med. 2019;8:1085

Characteristics of lipoproteins





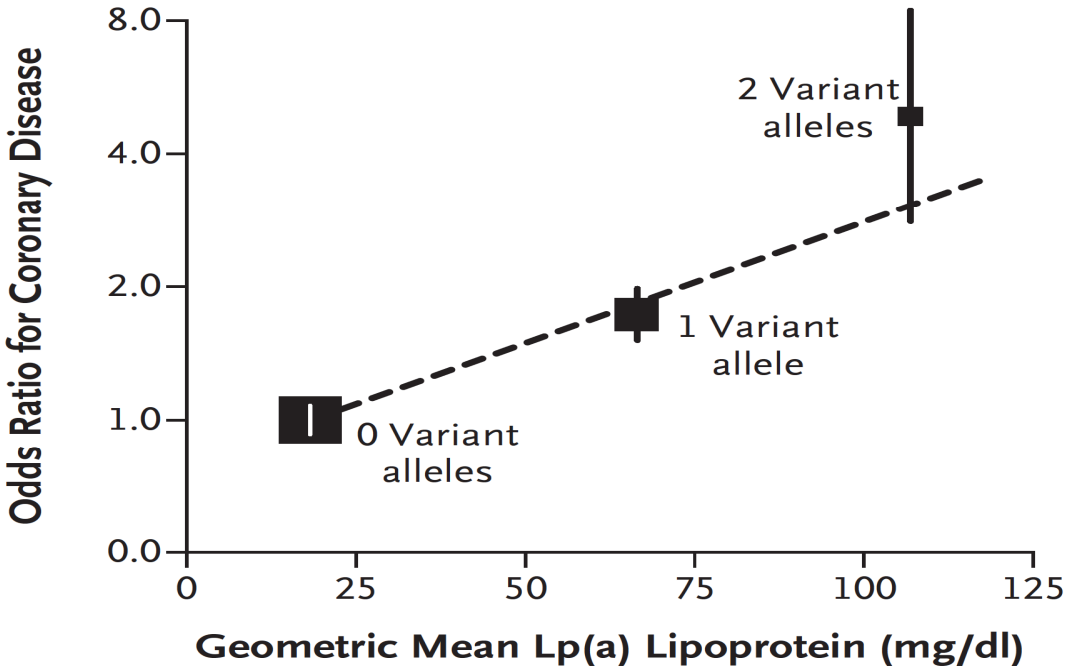
Lipoprotein(a)

Lipoprotein(a) and CV risk

ORIGINAL ARTICLE

Genetic Variants Associated with Lp(a) Lipoprotein Level and Coronary Disease

5% de la population générale !!!



New Engl J Med 2009;361:2518

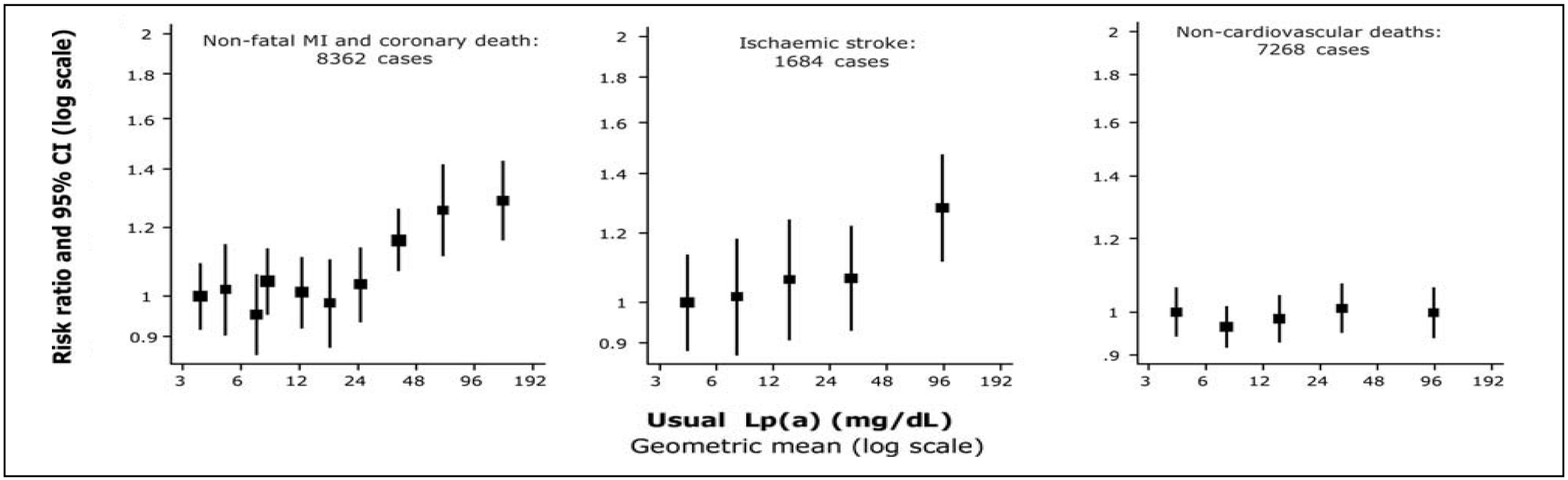
Lipoprotein(a) and CV risk

European Heart Journal (2010) **31**, 2844–2853
doi:10.1093/eurheartj/ehq386

CURRENT OPINION

Lipoprotein(a) as a cardiovascular risk factor: current status

Børge G. Nordestgaard[1*], M. John Chapman[2], Kausik Ray[3], Jan Borén[4], Felicita Andreotti[5], Gerald F. Watts[6], Henry Ginsberg[7], Pierre Amarenco[8], Alberico Catapano[9], Olivier S. Descamps[10], Edward Fisher[11], Petri T. Kovanen[12], Jan Albert Kuivenhoven[13], Philippe Lesnik[2], Luis Masana[14], Zeljko Reiner[15], Marja-Riitta Taskinen[16], Lale Tokgözoglu[17], and Anne Tybjærg-Hansen[18], for the European Atherosclerosis Society Consensus Panel[†]



Eur Heart J 2010;31:2844

Recommendations for lipid analysis

EAS ESC European Society of Cardiology

Recommendations for lipid analyses for cardiovascular disease risk estimation

Recommendations	Class[a]	Level[b]
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis method for screening, diagnosis, and management.	I	C
TG analysis is recommended as part of the routine lipid analysis process.	I	C
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

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

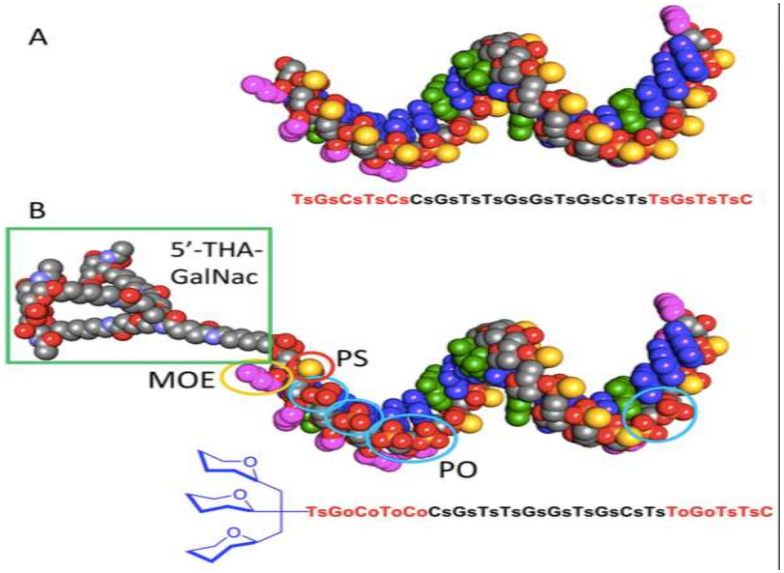
Lowering Lipoprotein(a) with apo(a)-antisense

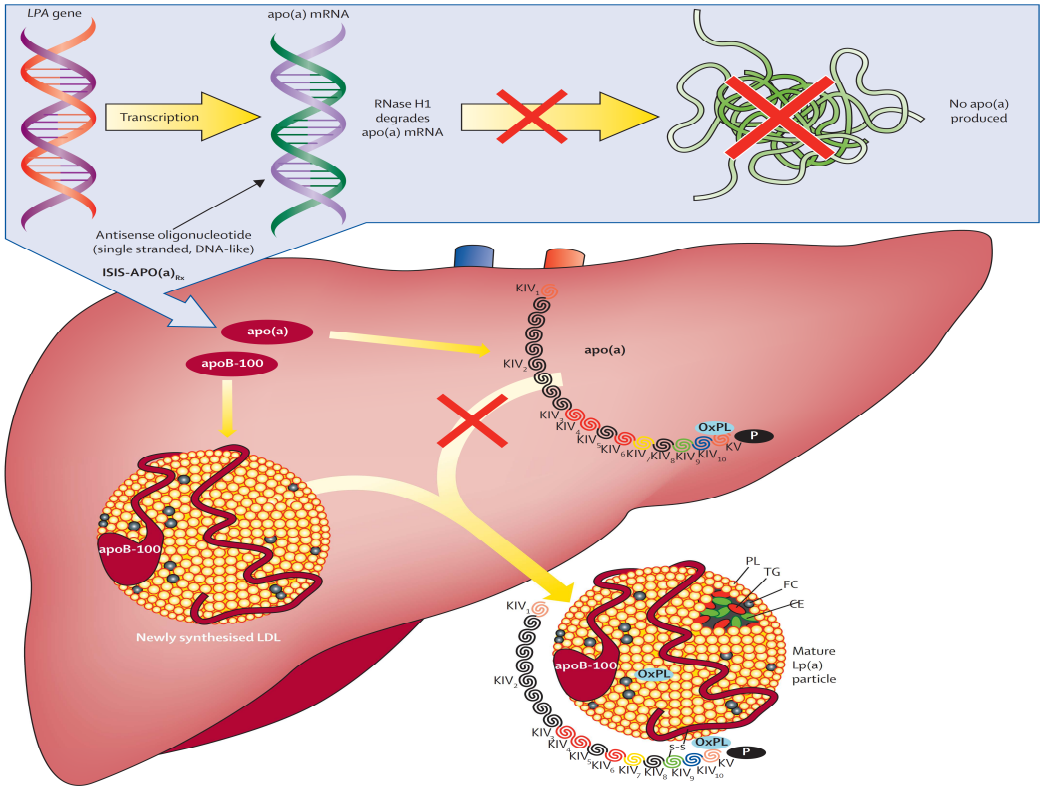
Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum

Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials

Nicholas J Viney, Julian C van Capelleveen, Richard S Geary, Shuting Xia, Joseph A Tami, Rosie Z Yu, Santica M Marcovina, Steven G Hughes, Mark J Graham, Rosanne M Crooke, Stanley T Crooke, Joseph L Witztum, Erik S Stroes, Sotirios Tsimikas





Lancet 2015;386:1472

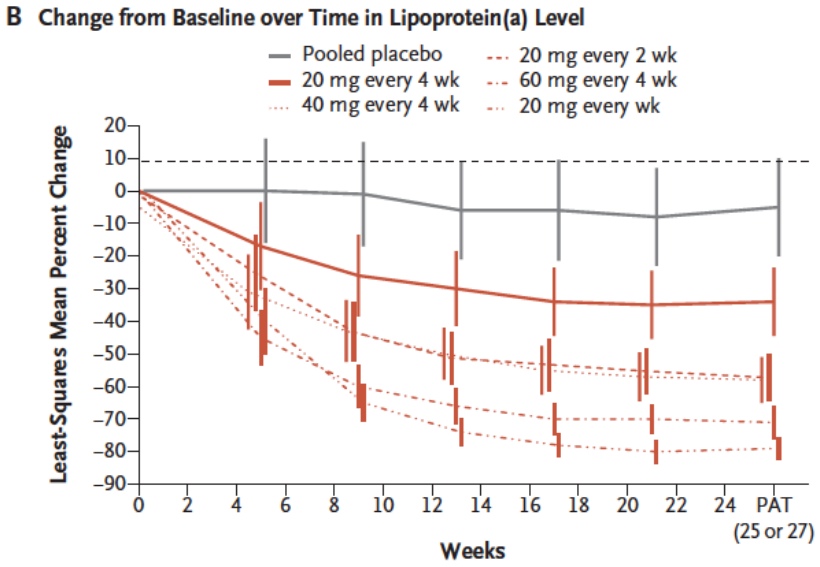
Lowering Lipoprotein(a) with apo(a)-antisense

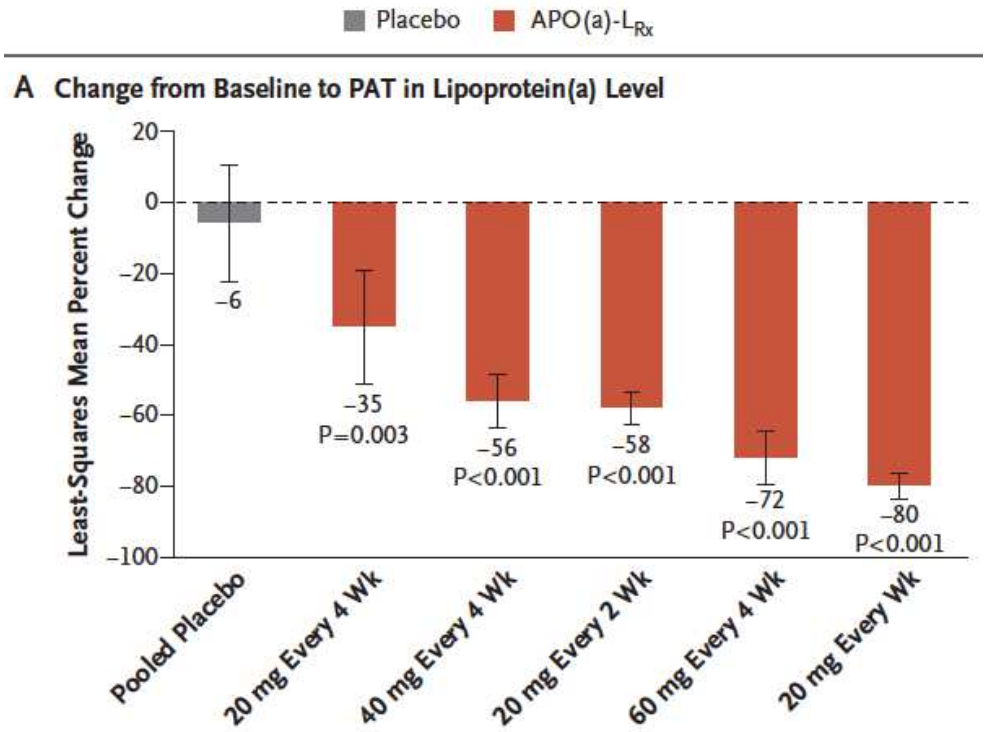
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lipoprotein(a) Reduction in Persons with Cardiovascular Disease

Sotirios Tsimikas, M.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Ioanna Gouni-Berthold, M.D., Jean-Claude Tardif, M.D., Seth J. Baum, M.D., Elizabeth Steinhagen-Thiessen, M.D., Michael D. Shapiro, D.O., Erik S. Stroes, M.D., Patrick M. Moriarty, M.D., Børge G. Nordestgaard, M.D., D.M.Sc., Shuting Xia, M.S., Jonathan Guerriero, M.B.A., Nicholas J. Viney, B.Sc., Louis O'Dea, M.B., B.Ch., B.A.O., and Joseph L. Witztum, M.D., for the AKCEA-APO(a)-L_{Rx} Study Investigators*





New Engl J Med 2020;382:244

Lowering Lp(a) with apo(a)-antisense – RCT

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Save this study

Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD (Lp(a)HORIZON)

ClinicalTrials.gov Identifier: NCT04023552

Study Description

Go to

Brief Summary:

This is a pivotal phase 3 study designed to support an indication for the reduction of cardiovascular risk in patients with established CVD and elevated Lp(a)

Condition or disease	Intervention/treatment	Phase
Cardiovascular Disease and Lipoprotein(a)	Drug: TQJ230 Drug: Placebo	Phase 3

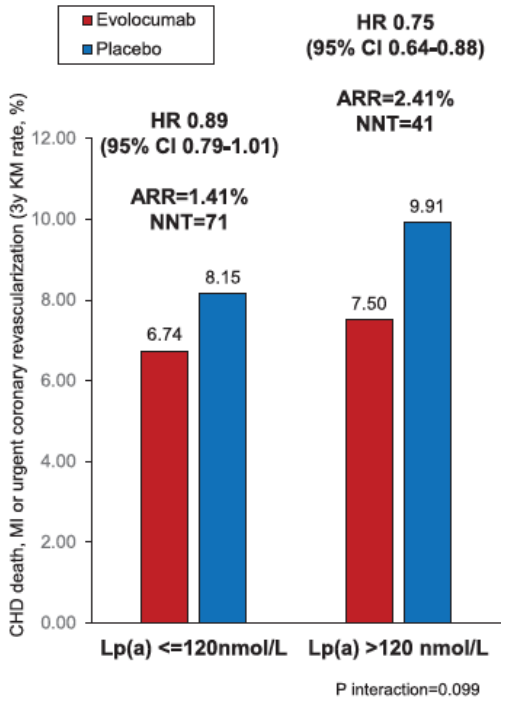
PCSK9 mAb (evolocumab)- Lp(a) and CV outcomes ?

Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

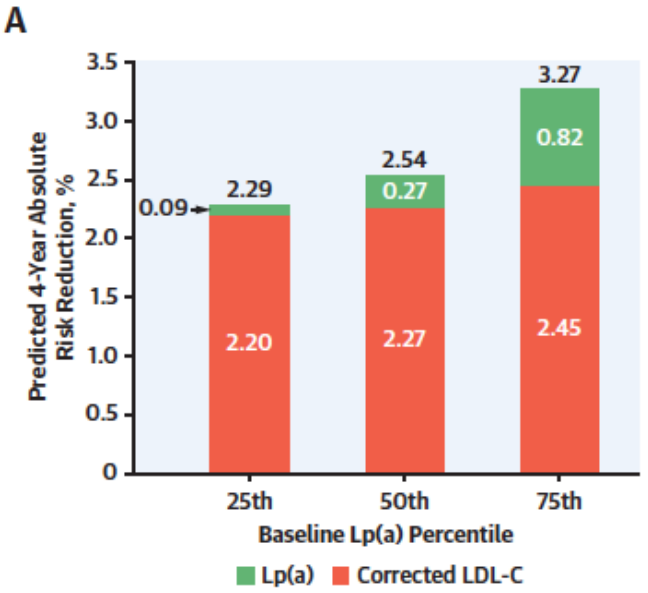
Insights From the FOURIER Trial



Circulation 2019;139:1483

ORIGINAL INVESTIGATIONS

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome



JACC 2020;75:133

Inclisiran and Lp(a)

Circulation

ORIGINAL RESEARCH ARTICLE

Effect of an siRNA Therapeutic Targeting PCSK9 on Atherogenic Lipoproteins

Prespecified Secondary End Points in ORION 1

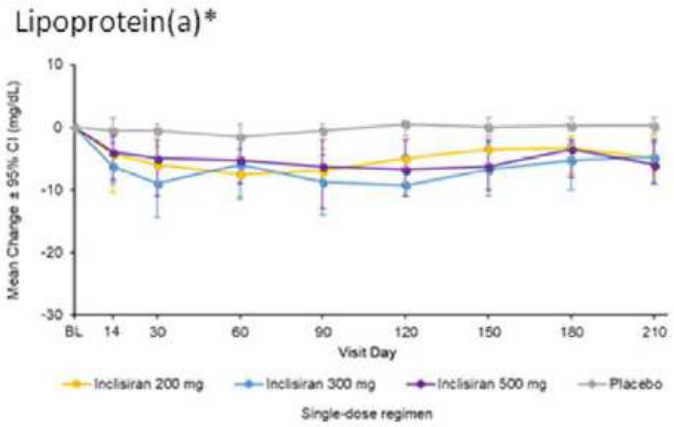
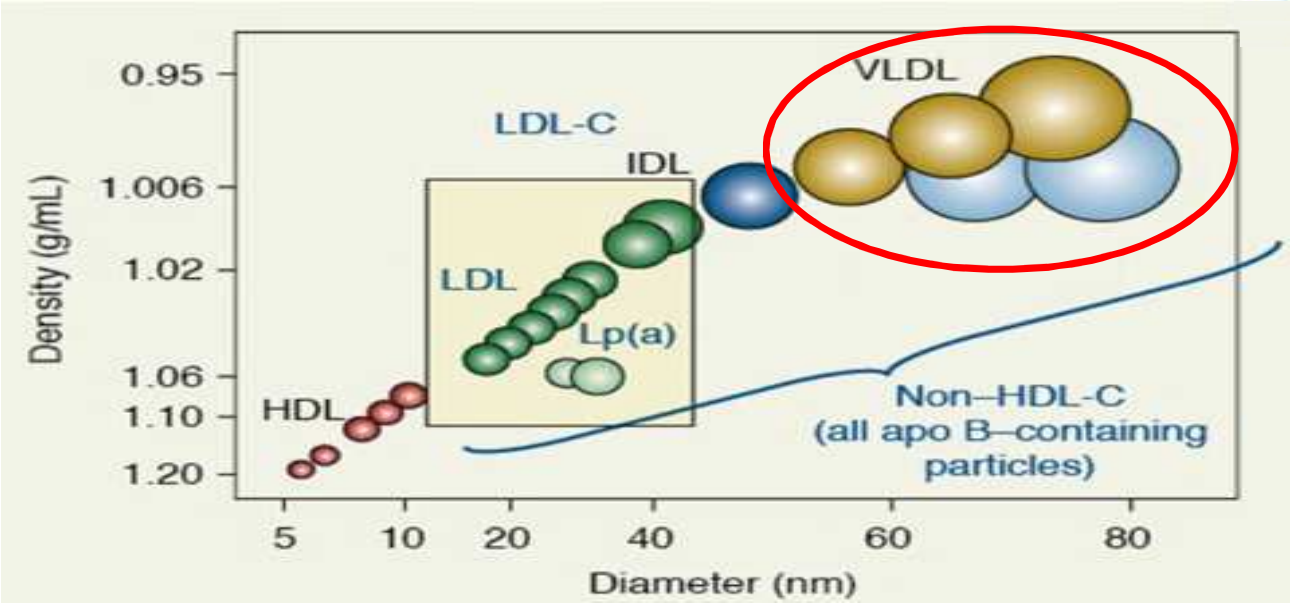


Table 2. Lipids and Lipoproteins at Baseline and Day 180*

	Single-Dose Groups				Double-Dose Groups			
	Placebo (n=64)	200 mg Inclisiran (n=60)	300 mg Inclisiran (n=60)	500 mg Inclisiran (n=60)	Placebo (n=61)	100 mg Inclisiran (n=59)	200 mg Inclisiran (n=60)	300 mg Inclisiran (n=59)
LDL-C								
Baseline	127.2 (52.31)	122.5 (34.73)	119.5 (41.56)	138.1 (46.05)	124.9 (44.20)	127.9 (47.85)	137.1 (70.98)	131.8 (58.51)
Day 180	127.8 (48.77)	87.7 (38.98)	75.2 (44.65)	82.4 (36.57)	124.1 (39.57)	82.9 (40.36)	82.0 (70.13)	67.6 (55.81)
Lp(a)								
Baseline	25.3 (8.5–122.0)	43.0 (11.0–127.0)	36.8 (18.8–147.0)	33.3 (10.8–151.5)	44.5 (12.0–146.0)	32.0 (11.5–134.0)	41.0 (9.8–140.3)	47.0 (11.0–160.5)
Day 180	22.0 (9.0–138.0)	29.5 (9.0–22.5)	31.5 (14.0–125.0)	19.5 (8.0–145.0)	52.0 (9.0–148.0)	29.0 (7.0–103.0)	32.0 (6.0–132.5)	36.0 (8.0–130.0)

Circulation 2018;138:1304

Characteristics of lipoproteins



Apo-CIII contaning particules, remnant cholesterol

Lowering Remnant cholesterol with Apo-CIII-antisense

The NEW ENGLAND JOURNAL of MEDICINE

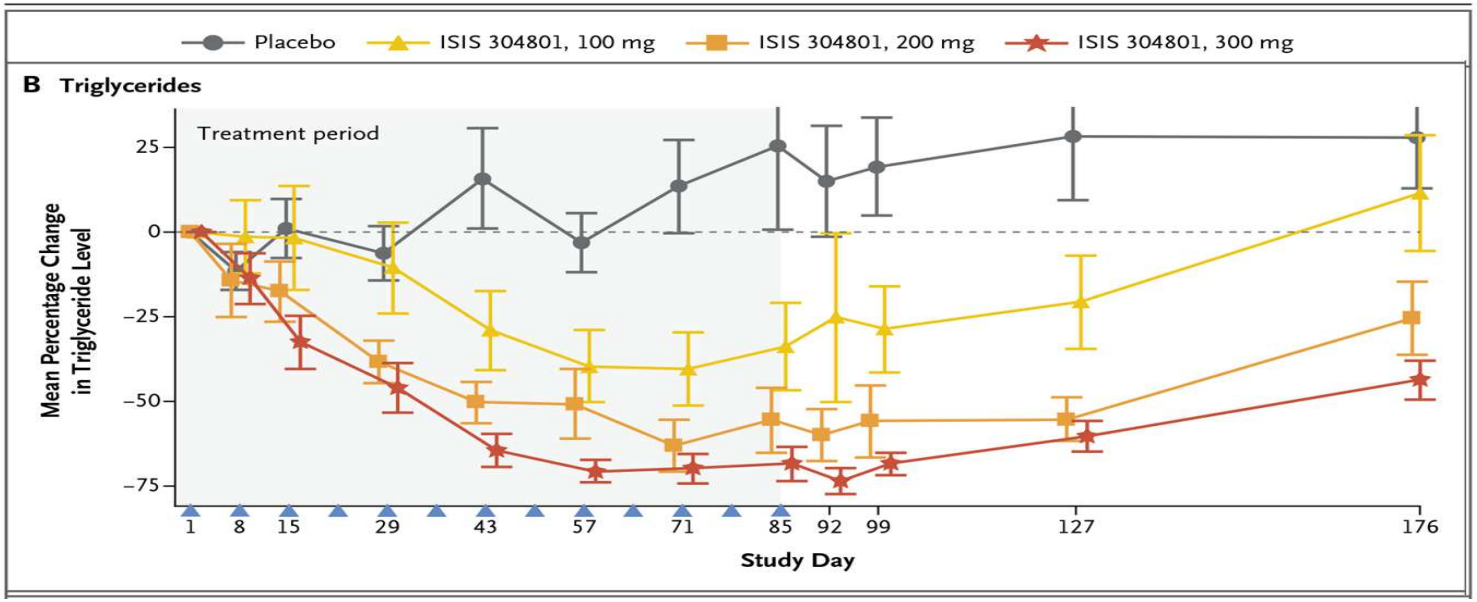
ORIGINAL ARTICLE

Cardiovascular and Metabolic Effects of *ANGPTL3* Antisense Oligonucleotides

Mark J. Graham, M.S., Richard G. Lee, Ph.D., Teresa A. Brandt, Ph.D., Li-Jung Tai, M.D., Ph.D., Wuxia Fu, M.S., Raechel Peralta, M.S., Rosie Yu, Ph.D., Eunju Hurh, Ph.D., Erika Paz, Bradley W. McEvoy, D.P.H., Brenda F. Baker, Ph.D., Nguyen C. Pham, B.S., Andres Digenio, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Joseph L. Witztum, M.D., Rosanne M. Crooke, Ph.D., and Sotirios Tsimikas, M.D.

'Remnant' cholesterol is next on the list

Apo-CIII antisense reduces TG and remnant cholesterol



New Engl J Med 2017;377:222

JAMA Network Open

Original Investigation | Cardiology

Statin Discontinuation and Cardiovascular Events Among Older People in Denmark

Abstract

IMPORTANCE Statin use is common in older persons. Given uncertainties in ongoing benefit, changes in health status, and shifting goals of care and preferences, statin discontinuation may be considered in some older persons, although there is currently little evidence to guide this decision.

OBJECTIVE To evaluate the association between statin discontinuation and the rate of major adverse cardiovascular events (MACE) among people aged 75 years or older who receive long-term statin treatment.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included all persons in Denmark aged 75 years or older who were treated with statins for at least 5 consecutive years as of January 1, 2011. Participants were followed up until December 31, 2016. Data were analyzed from July to November, 2020.

JAMA Network Open December 2021;4:e2136802

RESULTS The study included 67 418 long-term statin users, including 27 463 in the primary prevention analysis (median age, 79 years [IQR, 77-83 years]; 18 134 [66%] female) and 39 955 in the secondary prevention analysis (median age, 80 years [IQR, 77-84 years]; 18 717 [47%] female). In both primary and secondary prevention analyses, the rate of MACE was higher among persons who discontinued statins compared with those who continued statins. In the primary prevention cohort, the weighted rate difference was 9 per 1000 person-years (95% CI, 5-12 per 1000 person-years) and the adjusted sub-hazard ratio was 1.32 (95% CI, 1.18-1.48), corresponding to 1 excess MACE per 112 persons who discontinued statins per year. In the secondary prevention cohort, the weighted rate difference was 13 per 1000 person-years (95% CI, 8-17 per 1000 person-years) and the adjusted sub-hazard ratio was 1.28 (95% CI, 1.18-1.39), corresponding to 1 excess MACE per 77 persons who discontinued statins per year.

CONCLUSIONS AND RELEVANCE In this cohort study, among older adults receiving long-term statin treatment, discontinuation of statins was associated with a higher rate of MACE compared with statin continuation in both the primary and the secondary prevention cohorts. These findings suggest a need for robust evidence from randomized clinical trials.

JAMA Network Open December 2021;4:e2136802

Consultation “Lipides” aux HUG

- Consultation conjointe des **Services de Cardiologie** et **d’Endocrinologie**
  Prof. François Jornayvaz, Prof. Georg Ehret, Prof. François Mach
- Infirmière coordinatrice: Mme Elise Guillermet
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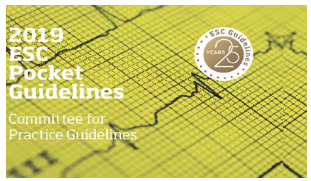
Hôpitaux Universitaires Genève

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

ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

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



ESC European Society of Cardiology EAS

Concept change I: Start early

Less "lipid-exposure" leads to prevention of lesion formation

Concept change II: Treat (much more) aggressively

From desirable target to "LDL-C elimination in the blood"

Concept change III: Use lipid-lowering combination therapy

Statin +/- ezetimibe +/- acid bempedoic (+/- PCSK9mAb) induced LDL-C lowering reduces CV risk

Concept change IV: The lower, the better & lower for longer

Statin +/- ezetimibe + siRNA induced LDL-C lowering with great efficacy, safety and full adherence

REMED
Réseau de Médecins - Genève

Merci pour votre attention