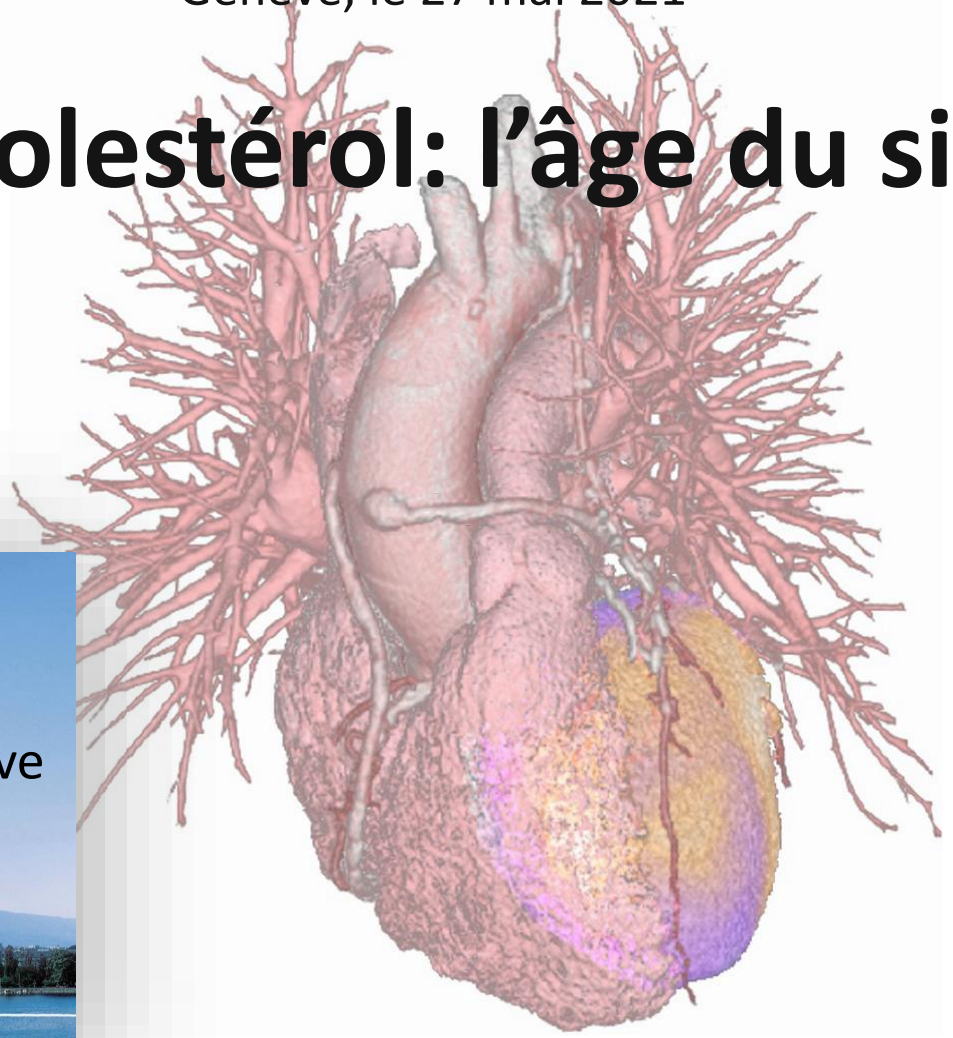
Service de cardiologie / HUG
Colloque multidisciplinaire de formation continue, cardiologie et chirurgie cardio-vasculaire
Genève, le 27 mai 2021

LDL-cholestérol: l'âge du silence



Prof. François Mach, MD, FESC
Service de Cardiologie
Hôpitaux Universitaires de Genève
francois.mach@hcuge.ch

Service de Cardiologie

HUG Hôpitaux Universitaires Genève

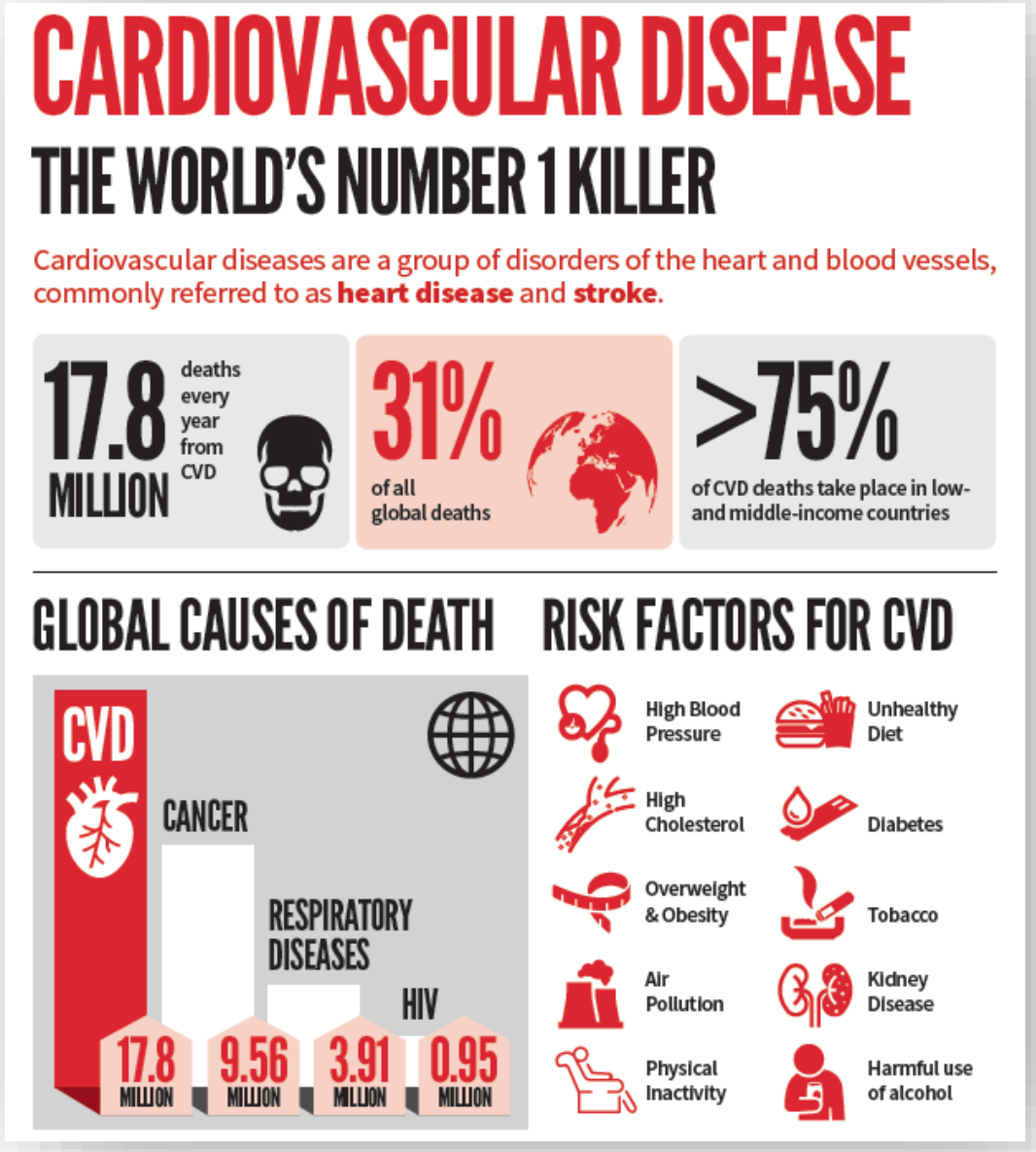
UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

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.

Maladies cardiovasculaires



Athérosclérose

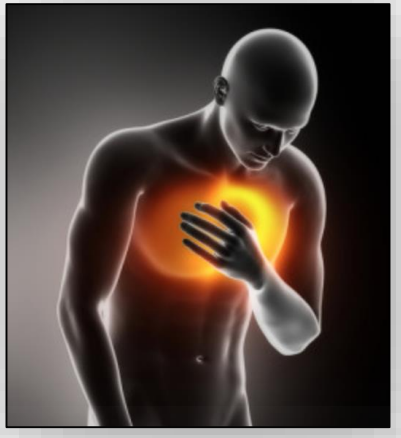
Coronary Artery Disease

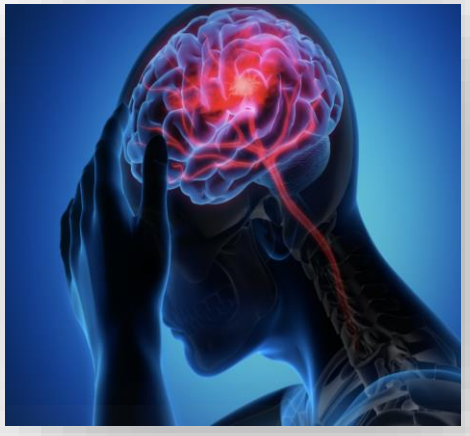
- Leading cause of mortality
- Happened globally
- Increase new cases
- Leading cause of loss of productivity

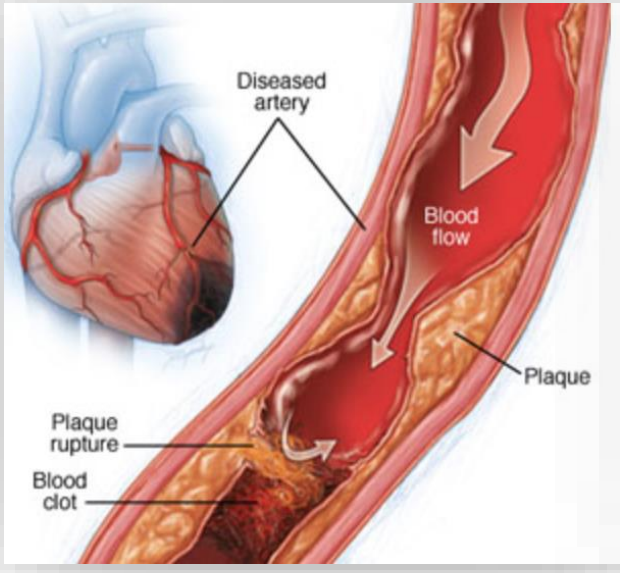
TRUE PANDEMIC

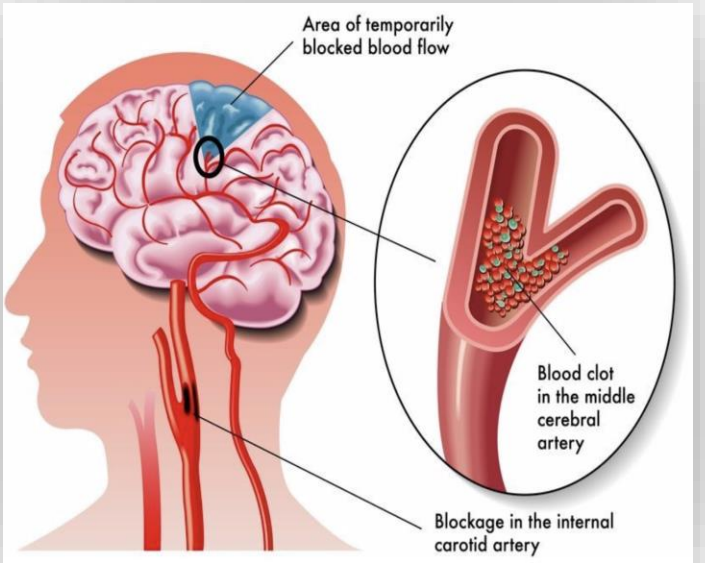
WHO (2009):

"CHD is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders"

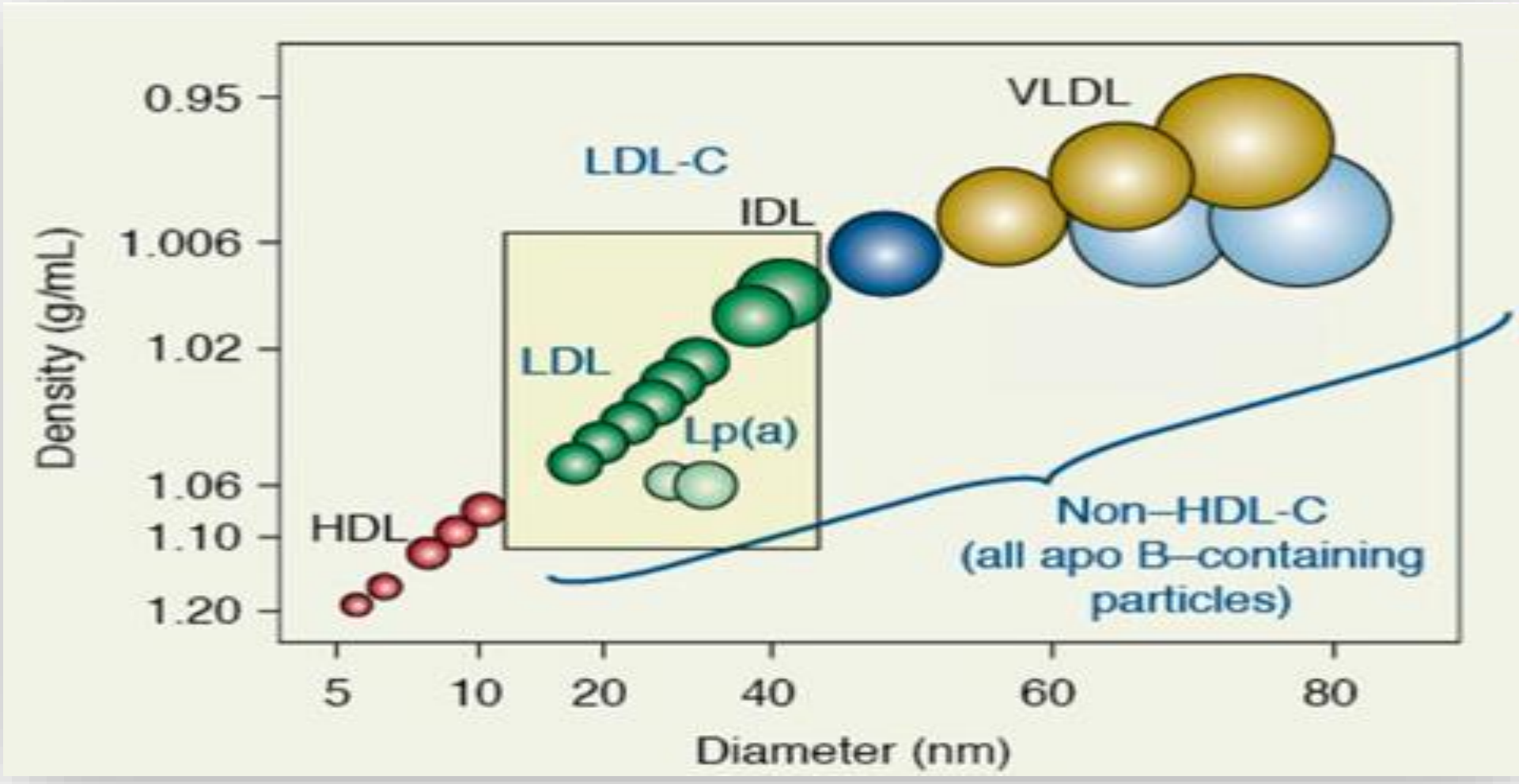








Caracteristiques des lipoprotéines

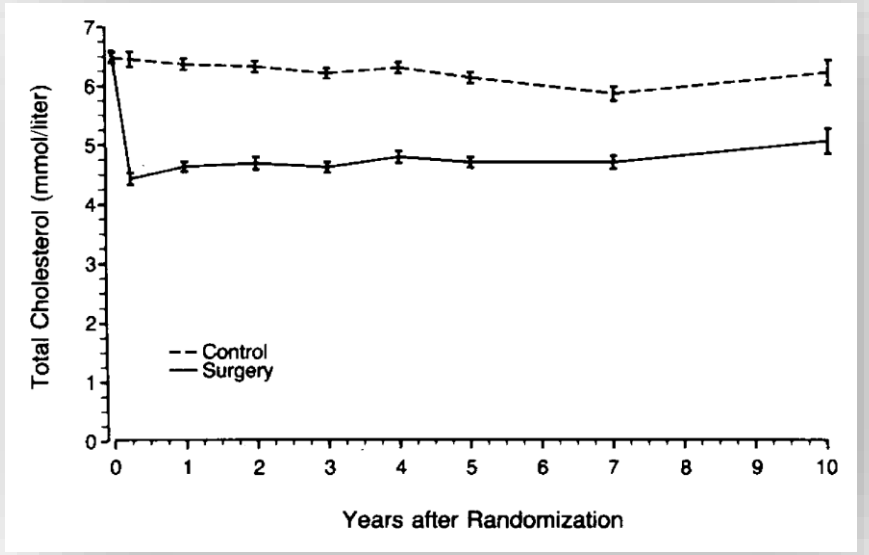


Lowering cholesterol lowers CV events: first evidence

EFFECT OF PARTIAL ILEAL BYPASS SURGERY ON MORTALITY AND MORBIDITY FROM CORONARY HEART DISEASE IN PATIENTS WITH HYPERCHOLESTEROLEMIA

Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH)

HENRY BUCHWALD, M.D., PH.D., RICHARD L. VARCO, M.D., PH.D., JOHN P. MATTS, PH.D., JOHN M. LONG, ED.D., LAURIE L. FITCH, M.P.H., GILBERT S. CAMPBELL, M.D., PH.D., MALCOLM B. PEARCE, M.D., ALBERT E. YELLIN, M.D., W. ALLAN EDMISTON, M.D., ROBERT D. SMINK, JR., M.D., HENRY S. SAWIN, JR., M.D., CHRISTIAN T. CAMPOS, M.D., BETTY J. HANSEN, R.N., NAIP TUNA, M.D., PH.D., JAMES N. KARNEGIS, M.D., PH.D., MIGUEL E. SANMARCO, M.D., KURT AMPLATZ, M.D., WILFREDO R. CASTANEDA-ZUNIGA, M.D., DAVID W. HUNTER, M.D., JOSEPH K. BISSETT, M.D., FREDERIC J. WEBER, M.D., PH.D., JAMES W. STEVENSON, M.D., ARTHUR S. LEON, M.D., THOMAS C. CHALMERS, M.D., AND THE POSCH GROUP*



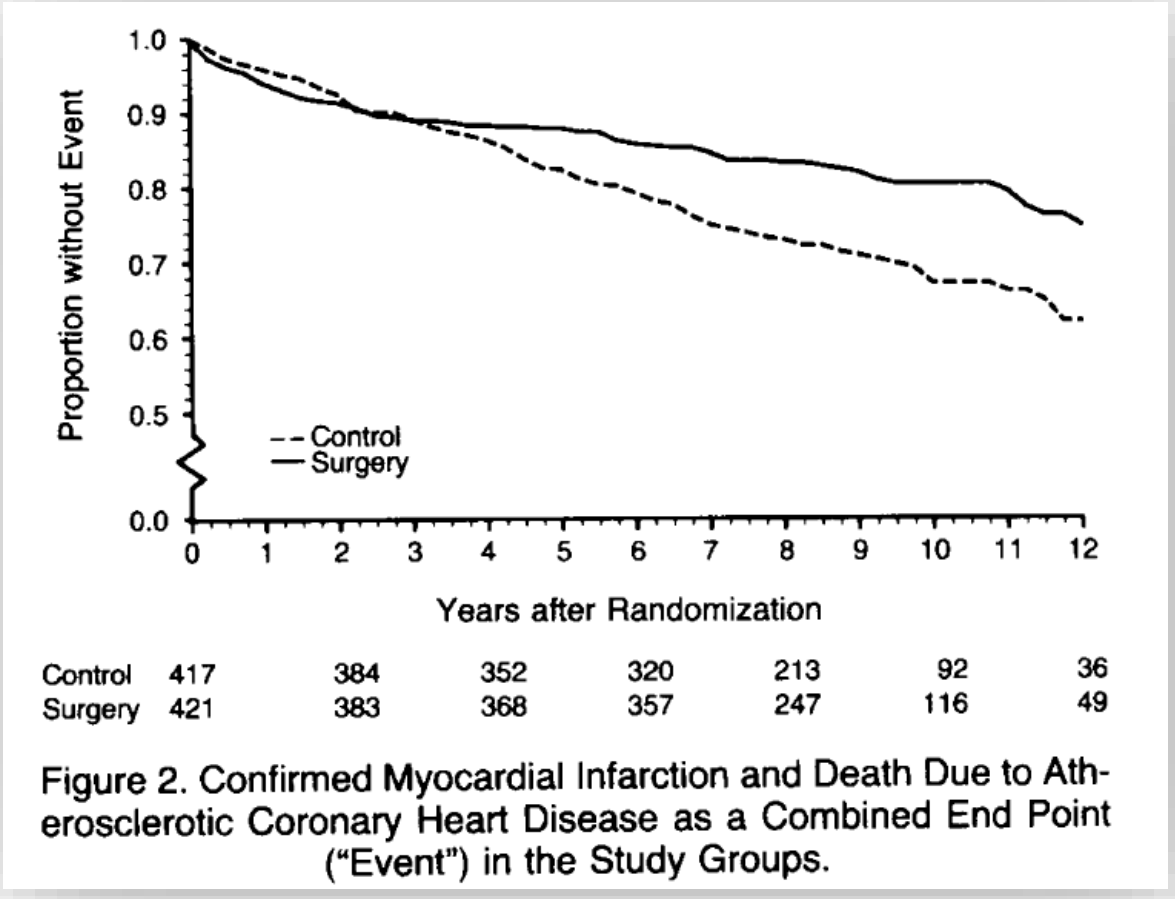
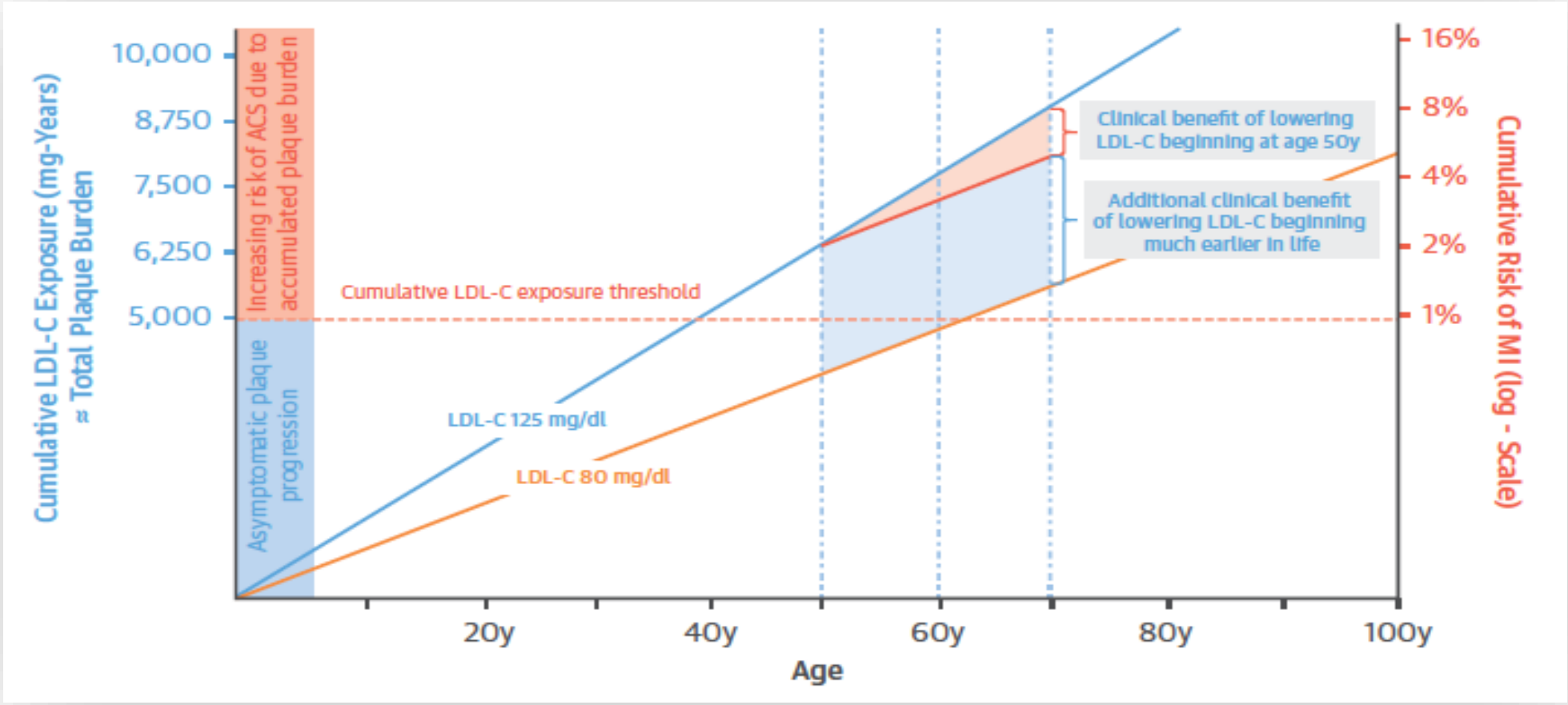


Figure 2. Confirmed Myocardial Infarction and Death Due to Atherosclerotic Coronary Heart Disease as a Combined End Point ("Event") in the Study Groups.

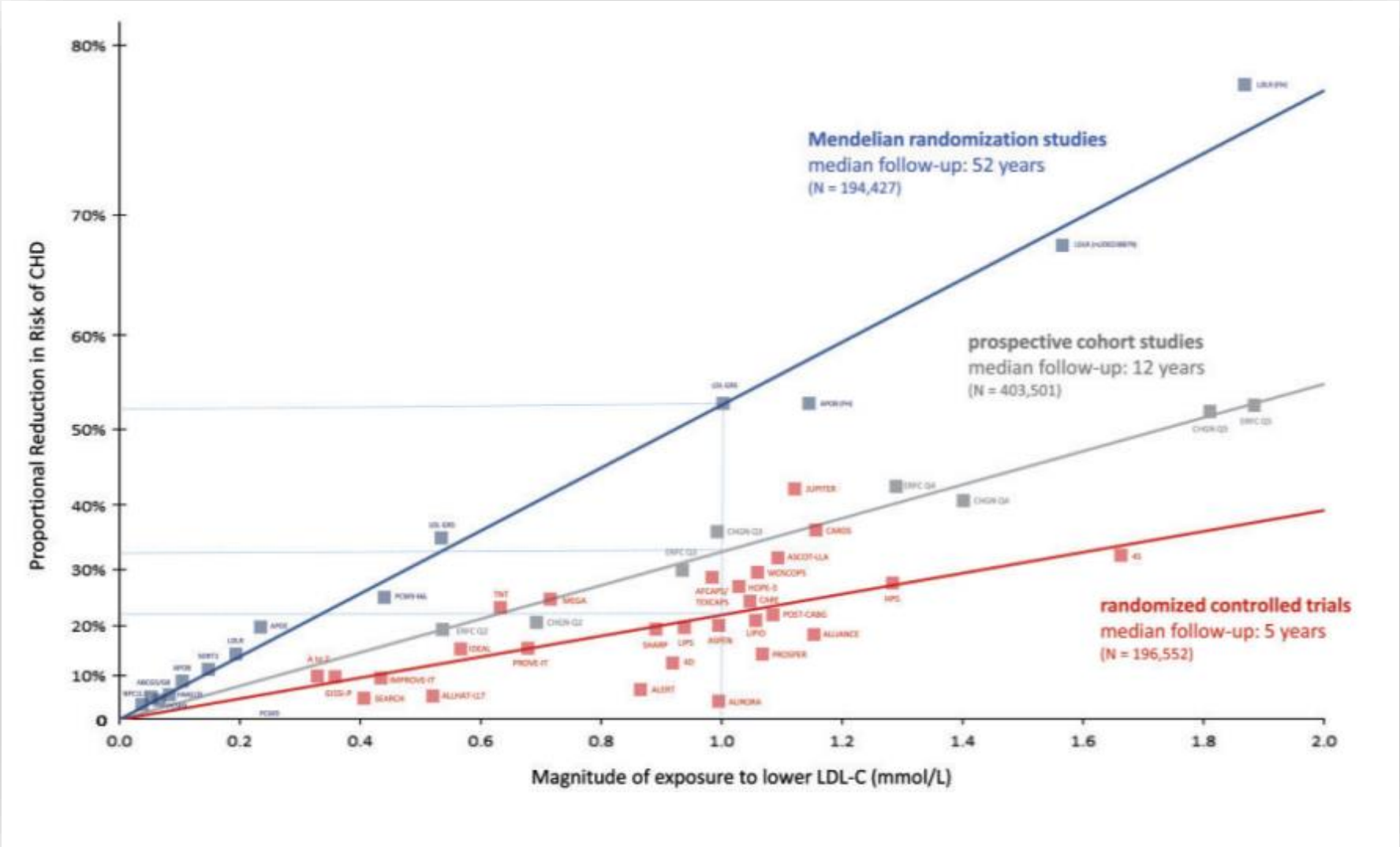
N Engl J Med 1990;323:946

Time-Exposure to LDL-C



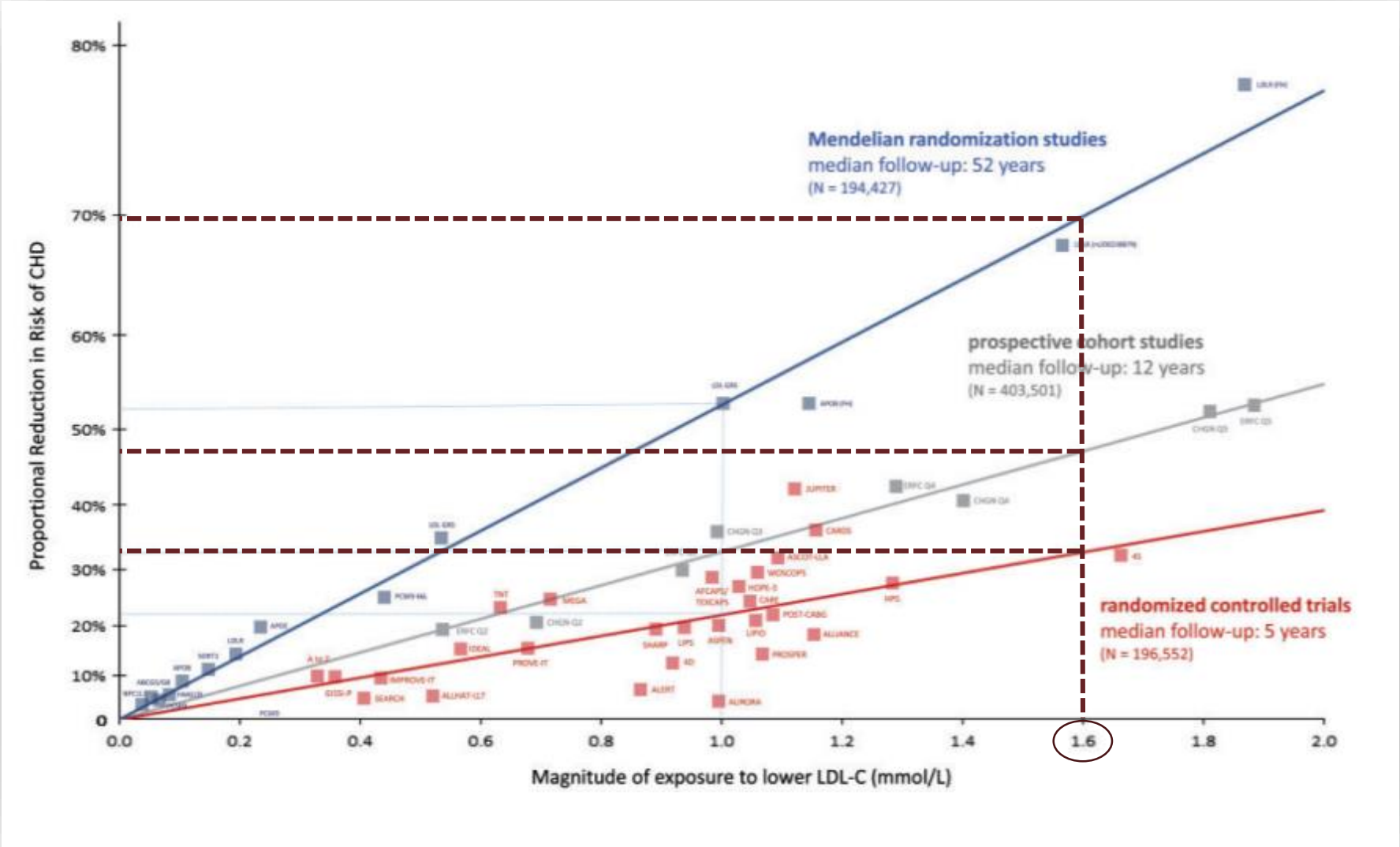
JACC 2018;72:2890

Time-Exposure to low LDL-C



Eur Heart J 2017;38:2459

Time-Exposure to low LDL-C



Eur Heart J 2017;38:2459

Evidence for efficacy of LDL-lowering therapies down to below 1.4 mmol/L (55 mg/dL)

EAS ESC European Society of Cardiology

Source of evidence	Mean reduction in LDL cholesterol; mmol/L [mg/dL]	Outcome	RR (95% CI)
CTT meta-analysis[1] (high-intensity vs standard statin; subgroup <2.0 mmol/L)	1.71 [66] vs 1.32 [50]	MI, CHD death, stroke, coronary revasc.	0.71 (0.56-0.91) [per mmol/L]
IMPROVE-IT[2] (eze plus statin vs statin)	1.80 [70] vs 1.40 [54]	CV death, MI, stroke, UA, coronary revasc	0.94 (0.89-0.99)
FOURIER[3] (evolocumab plus high-dose statin ± eze vs high-dose statin ± eze)	2.37 [92] vs 0.78 [30]	CV death, MI, stroke, UA, coronary revasc	0.85 (0.79-0.92)
ODYSSEYOUTCOMES[4] (alirocumab plus high-dose statin ± eze vs high-dose statin ± eze)	2.37 [92] vs 1.37 [53]	MI, CHD death, stroke, UA	0.85 (0.78-0.93)

[1]*Lancet* 2010;376:1670; [2]*NEJM* 2015;372:2387; [3]*NEJM* 2017;376:1713; [4]*NEJM* 2018;379:2097

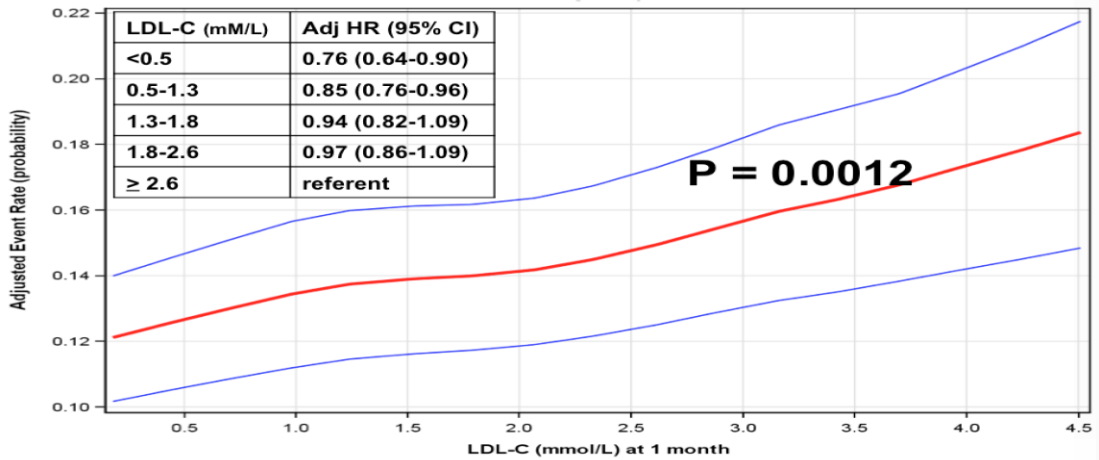
PCSK9 mAb: Efficacy and safety

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

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

Primary Efficacy Endpoint*

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



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

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

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

Lancet 2017;390:1962

ESC/EAS 2019 Lipid Guidelines

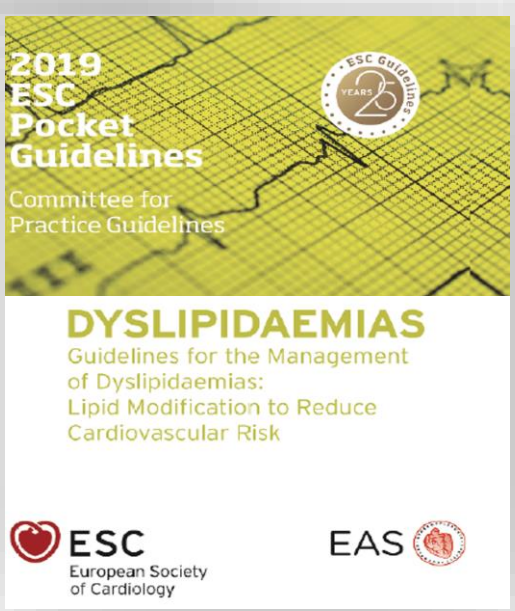
ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

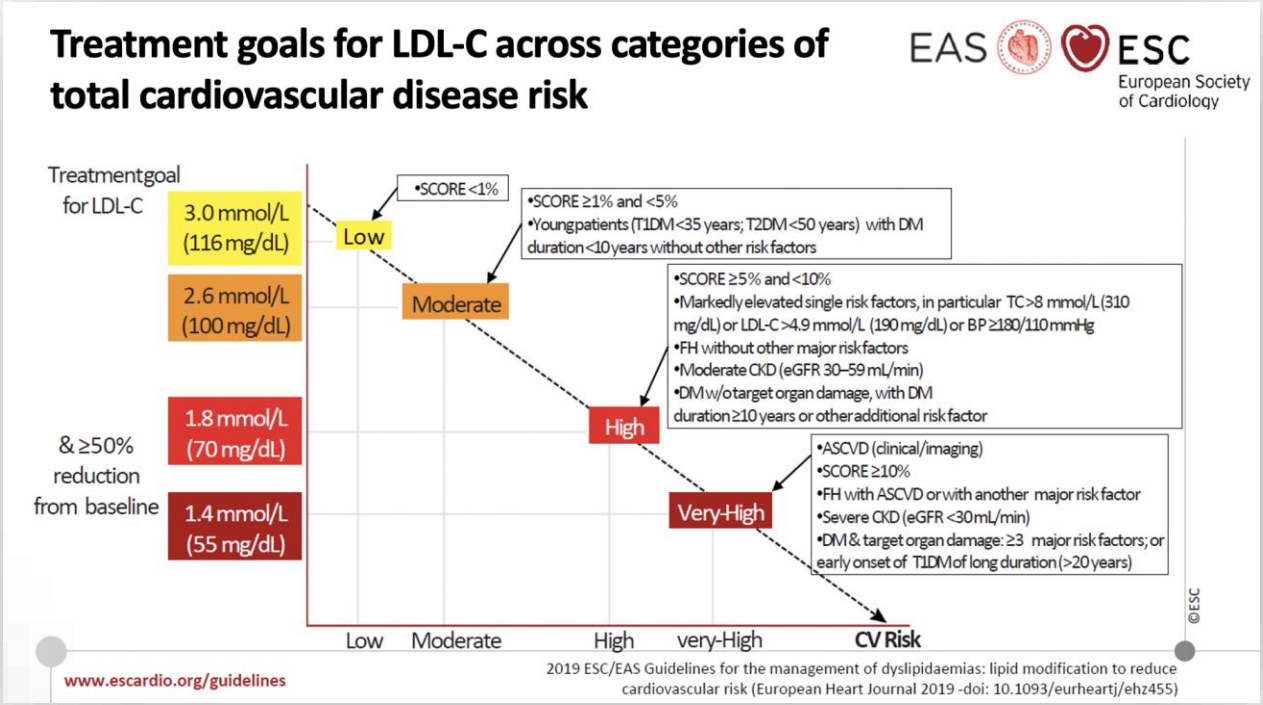
ESC/EAS GUIDELINES

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)

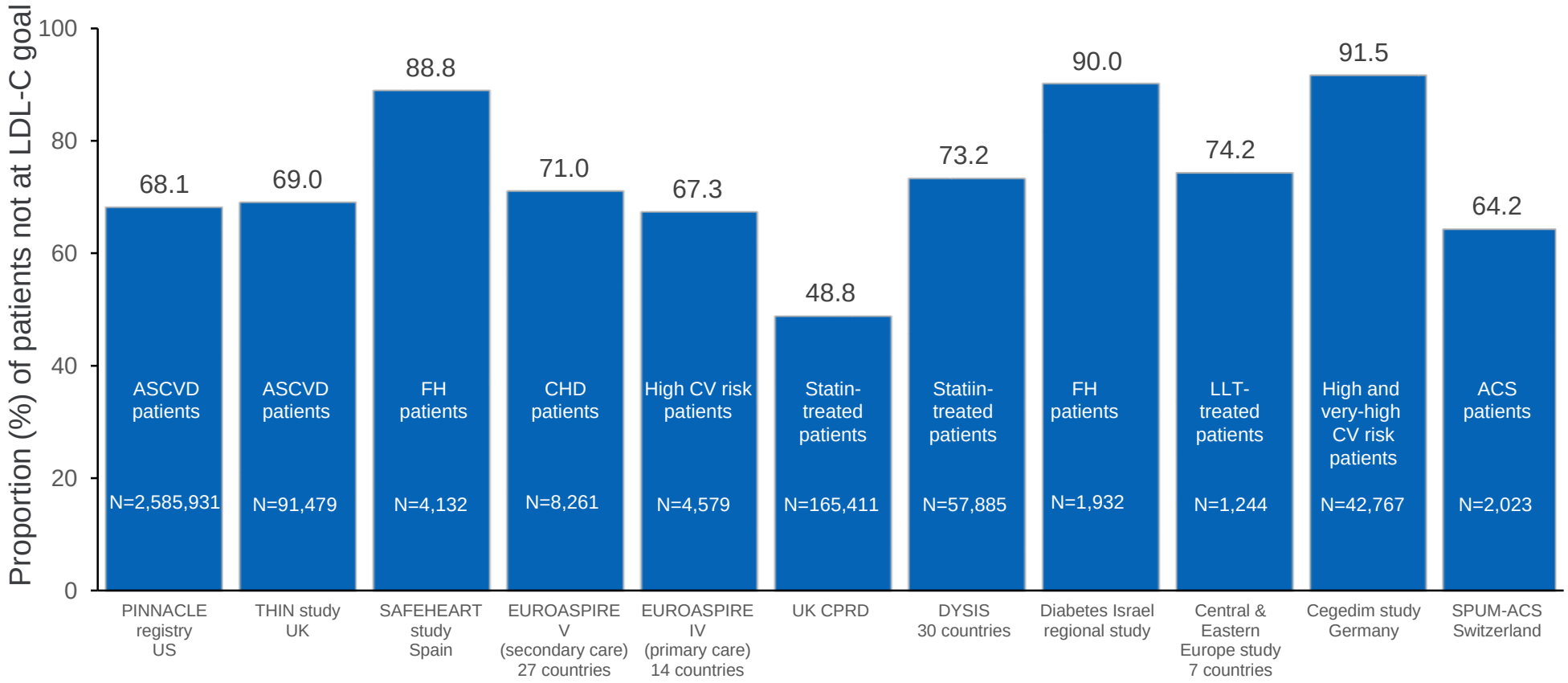
Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano[1]* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula[1] (Italy), Lina Badimon (Spain), M. John Chapman[1] (France), Guy G. De Backer (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)





Eur Heart J 2020;41:111

Despite efficacious LDL-C lowering therapies: High and very high-risk patients are failing to achieve LDL-C goals



Circulation. 2019;140 (S1):A12904; *BMJ Open.* 2017;7:e013255; *JACC.* 2016;67:1278; *Atherosclerosis.* 2019;285:135; *Eur J Prev Cardiol.* 2016;23:2007; *Heart.* [illegible]:01; *Atherosclerosis.* 2016;255:200; *Eur J Prev Cardiol.* 2017;24:867; *Adv Ther.* 2019;36:608; *Atherosclerosis.* 2018;268:99; *J Am Heart Assoc.* 2017;6:e0[illegible]537.

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

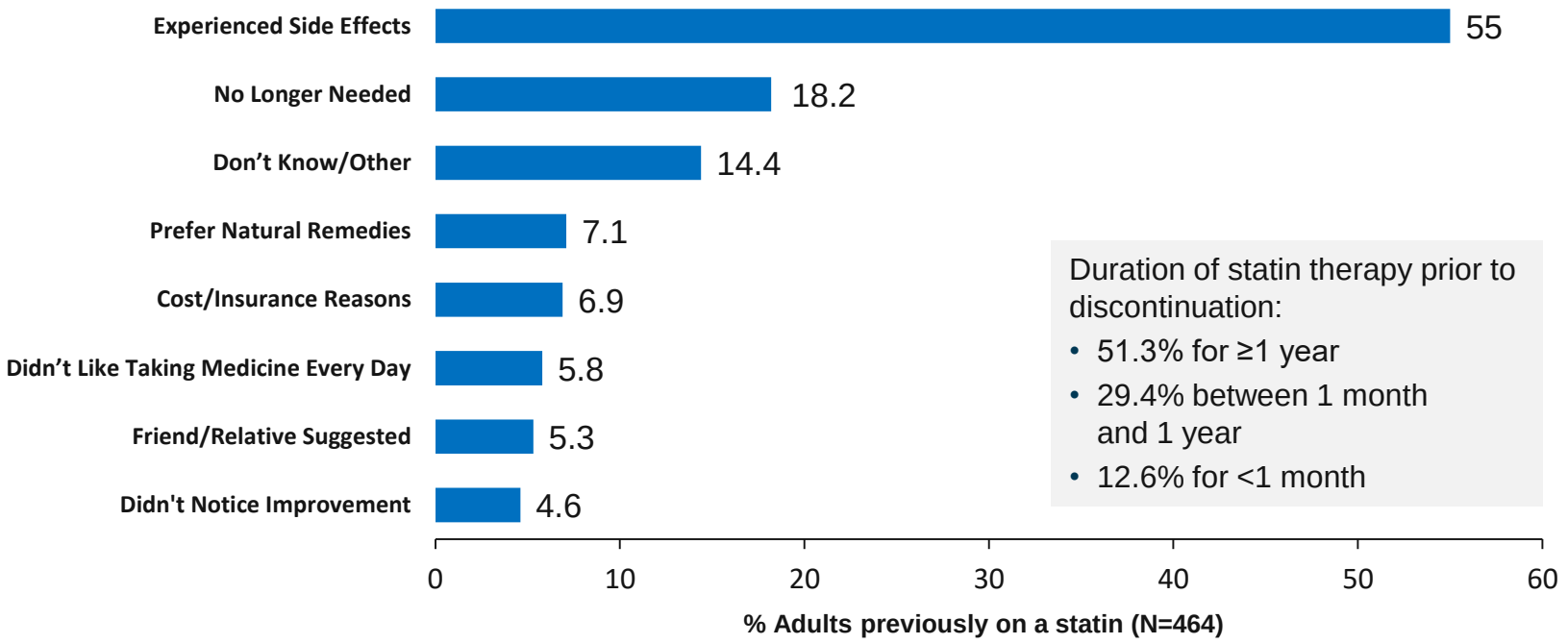
- Lack of HCP familiarity with guidelines
- High cost of medications such as PCSK9 mAb inhibitors
- Patient reluctance to be treated with high-intensity LLT
- Concern about statin-related AEs

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

Perceived side effects are the leading cause of statin discontinuation

Patient-reported reasons for statin discontinuation: insights from PALM registry



Duration of statin therapy prior to discontinuation:

- 51.3% for ≥1 year
- 29.4% between 1 month and 1 year
- 12.6% for <1 month

J Am Heart Assoc 2019;8:e011765

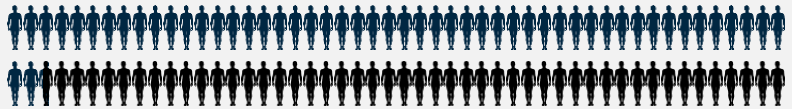
Therapy interruptions are observed with monoclonal antibodies directed against PCSK9

Retrospective analysis of 6151 patients from a commercial insurance database in the United States initiating PCSK9mAb inhibitors

52.2% of patients

experienced an interruption in PCSK9mAb inhibitor therapy of at least 30 days within 1 year of its initiation

- **Only 63%** remained on a PCSK9mAb inhibitor 1 year after its initiation



44% of patients

experienced an interruption in all lipid-lowering therapy by 1 year of initiation of PCSK9mAb inhibitor

- **27%** were no longer on any lipid-lowering therapy 1 year after initiating a PCSK9mAb inhibitor

J Am Heart Assoc 2019;9:e014347

Research on ACS management

Atherosclerosis Supplements 42 (2020) e49–e58

Contents lists available at ScienceDirect

Atherosclerosis Supplements

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

Lipid-lowering therapy and low-density lipoprotein cholesterol goal achievement in patients with acute coronary syndromes: The ACS patient pathway project

Ulf Landmesser [a], Angela Pirillo [b], Michel Farnier [c], J. Wouter Jukema [d], Ulrich Laufs [e], François Mach [f], Luis Masana [g], Terje R. Pedersen [h], François Schiele [i], Gabriel Steg [j], Marco Tubaro [k], Azfar Zaman [l], Pepe Zamorano [m], Alberico L. Catapano [n,*]

Atherosclerosis 2020;40:e49-e58

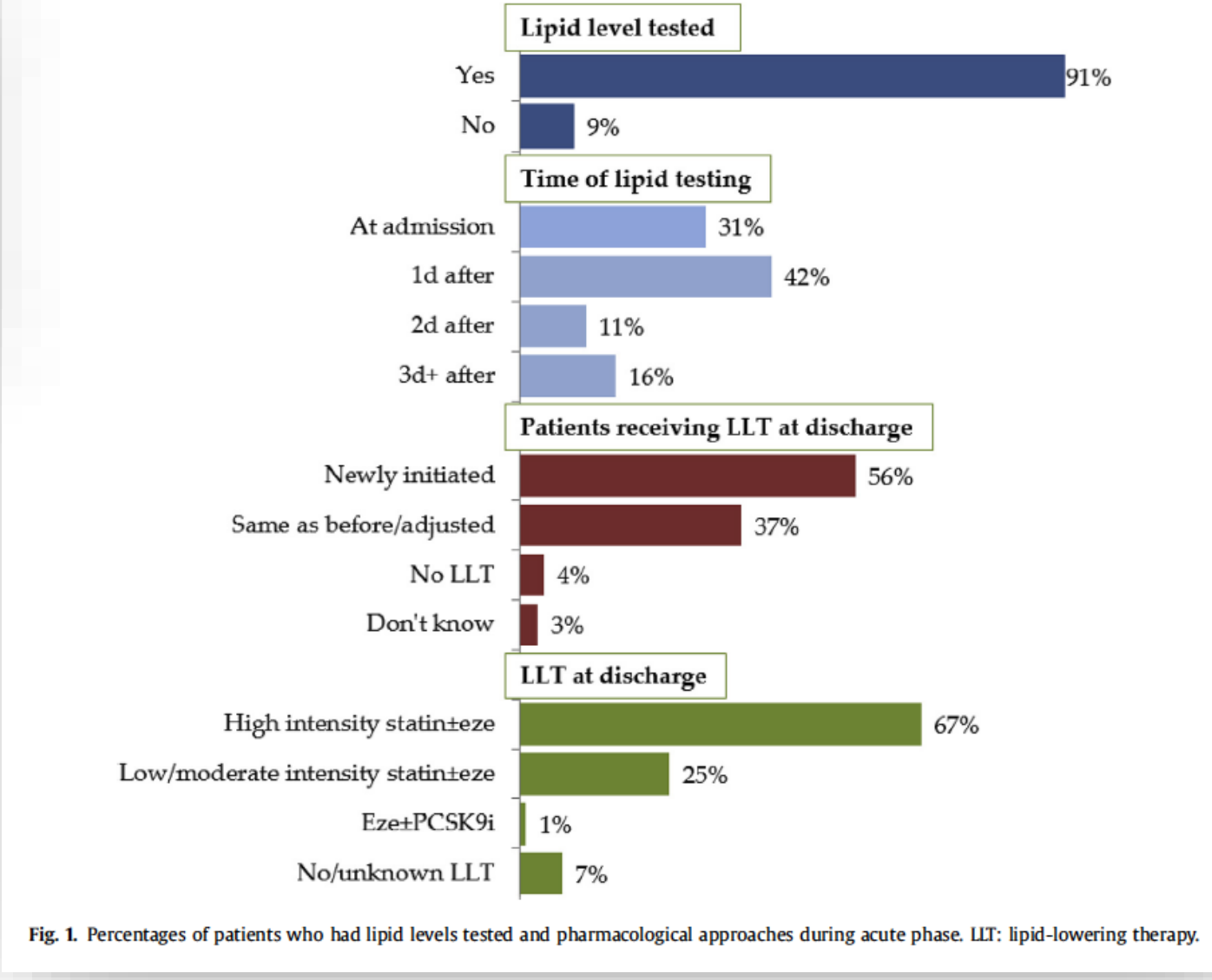


Fig. 1. Percentages of patients who had lipid levels tested and pharmacological approaches during acute phase. LLT: lipid-lowering therapy.

Research on ACS management

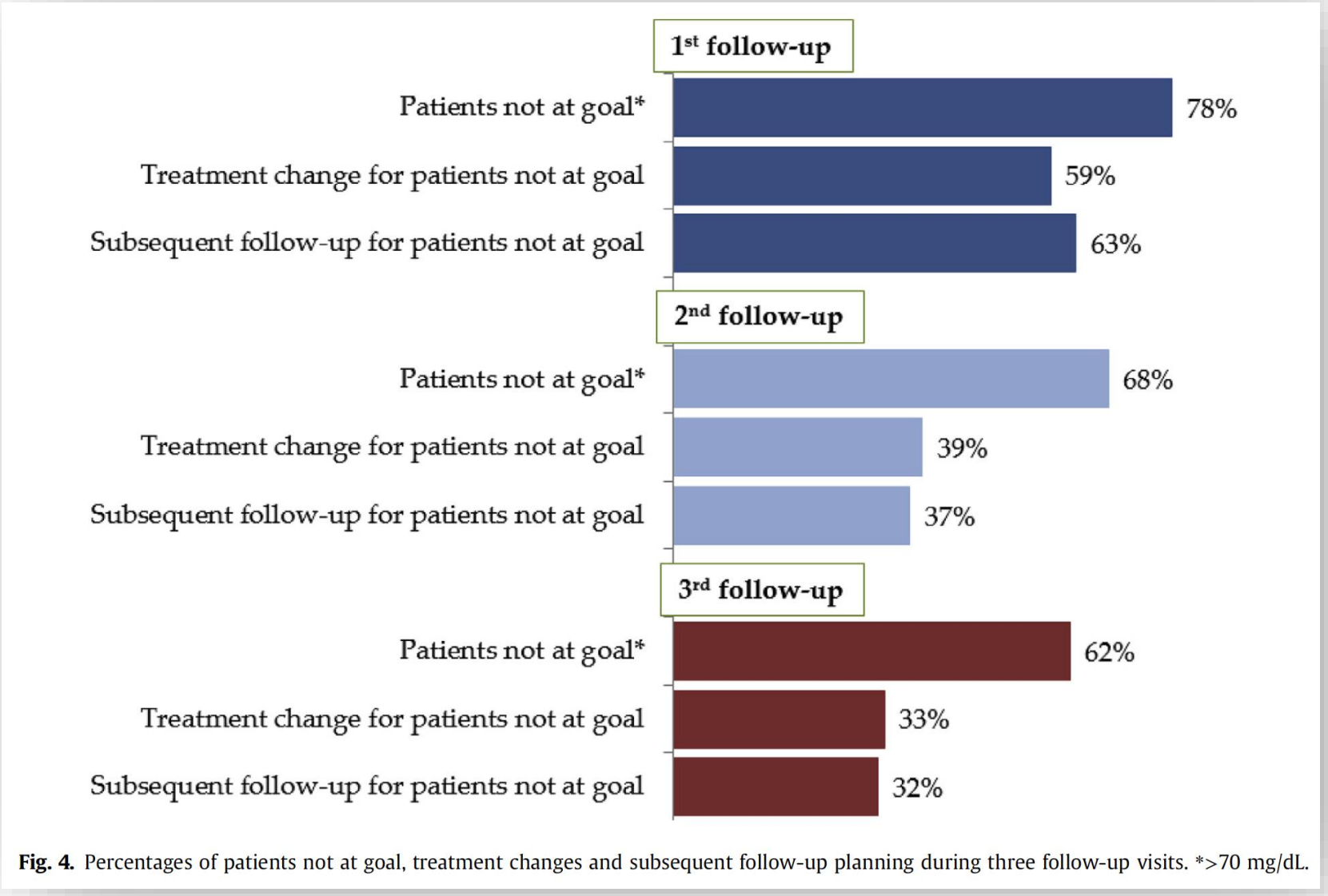


Fig. 4. Percentages of patients not at goal, treatment changes and subsequent follow-up planning during three follow-up visits. *>70 mg/dL.

Atherosclerosis 2020;40:e49-e58

Research on ACS management

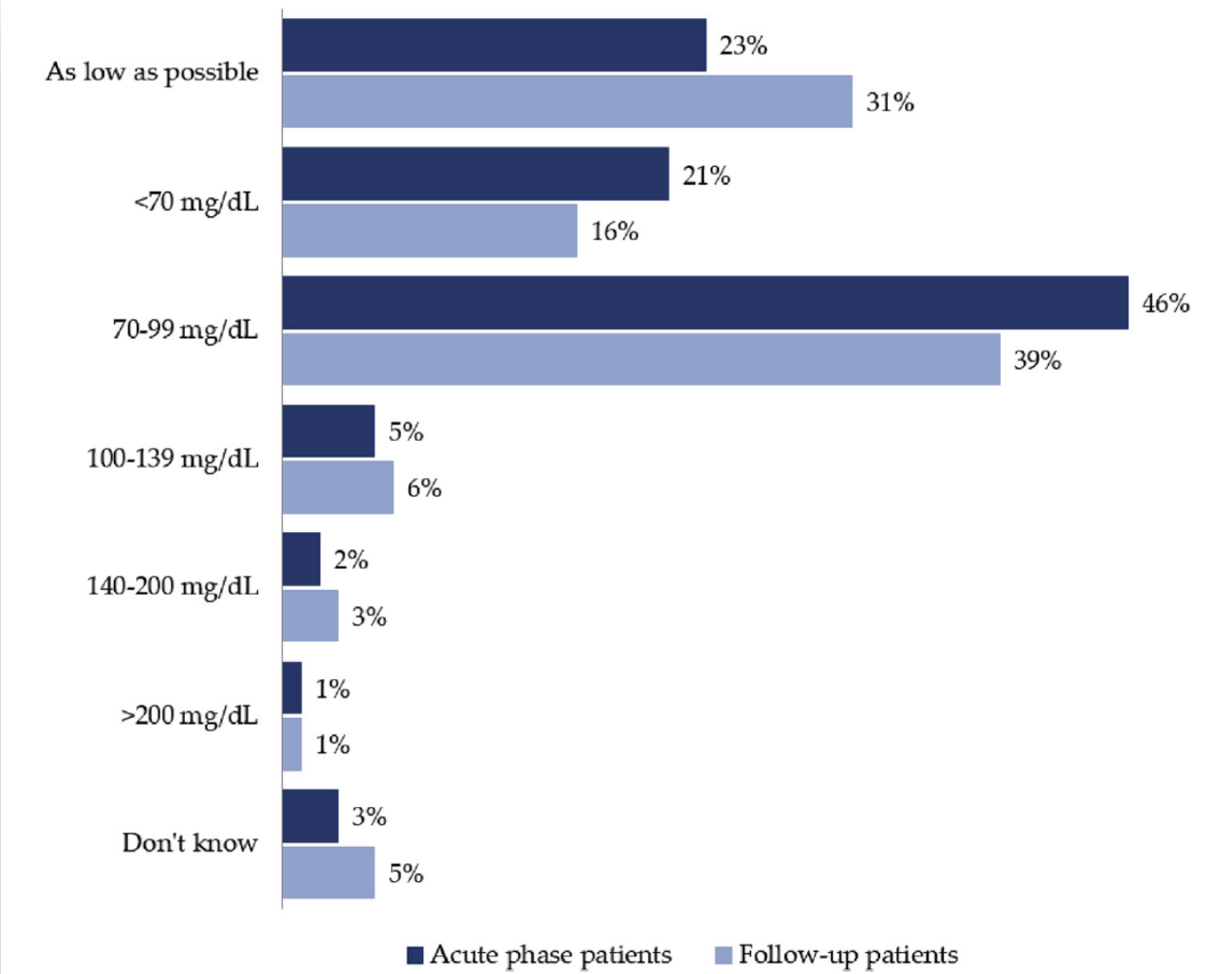
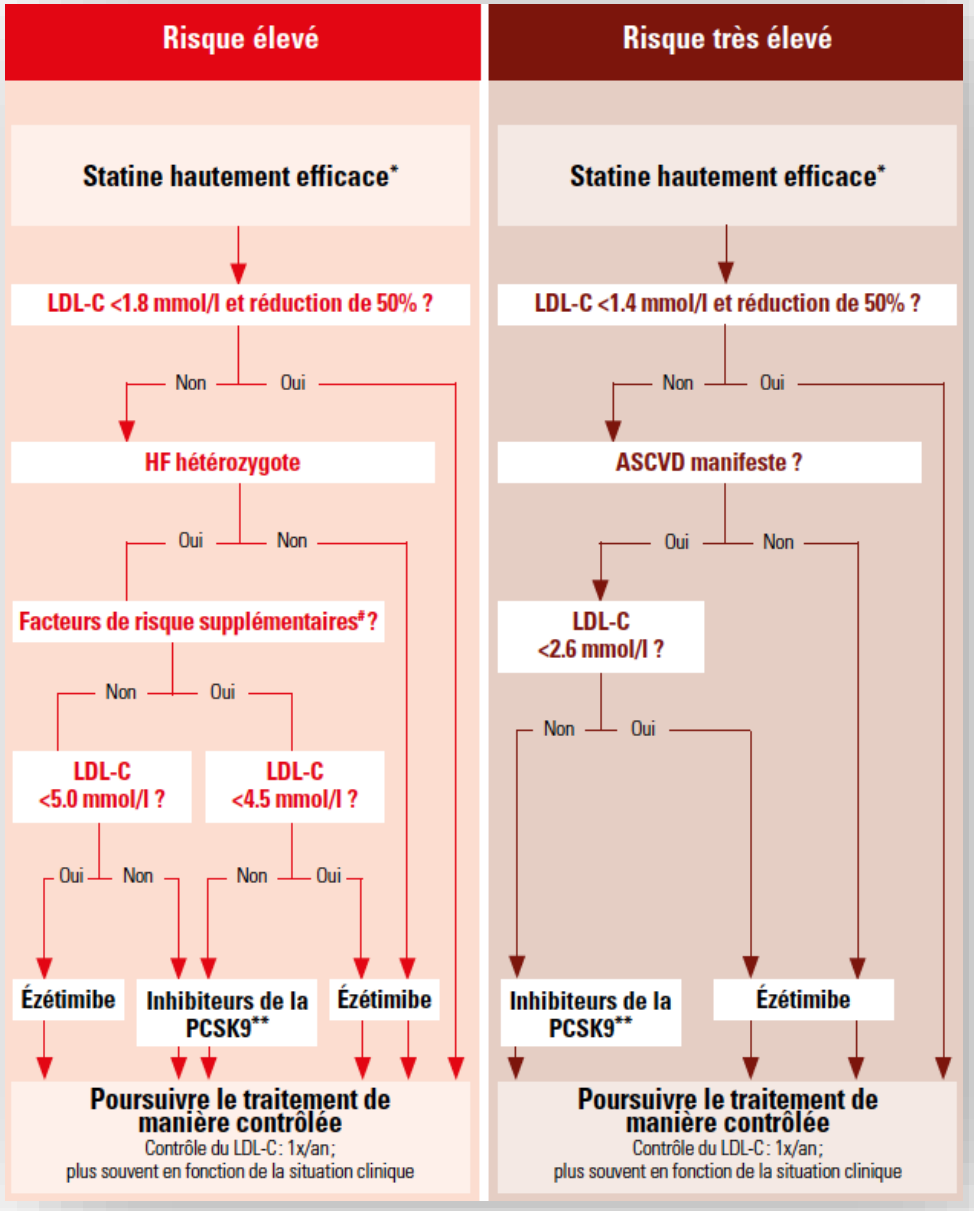


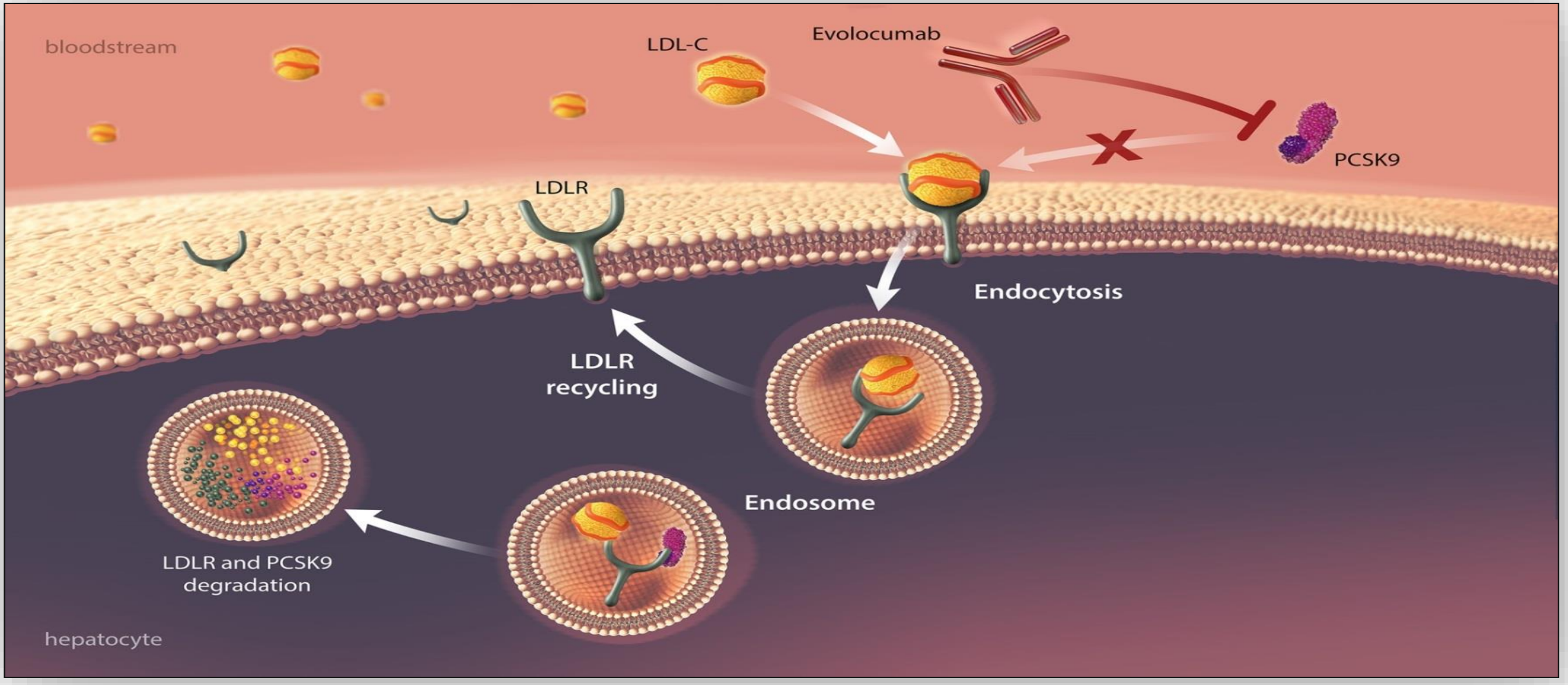
Fig. 6. LDL-C goal for acute phase and follow-up patients, as indicated by cardiologists during the survey.

Atherosclerosis 2020;40:e49-e58

AGLA/GSLA lipid guidelines (www.agla.ch)

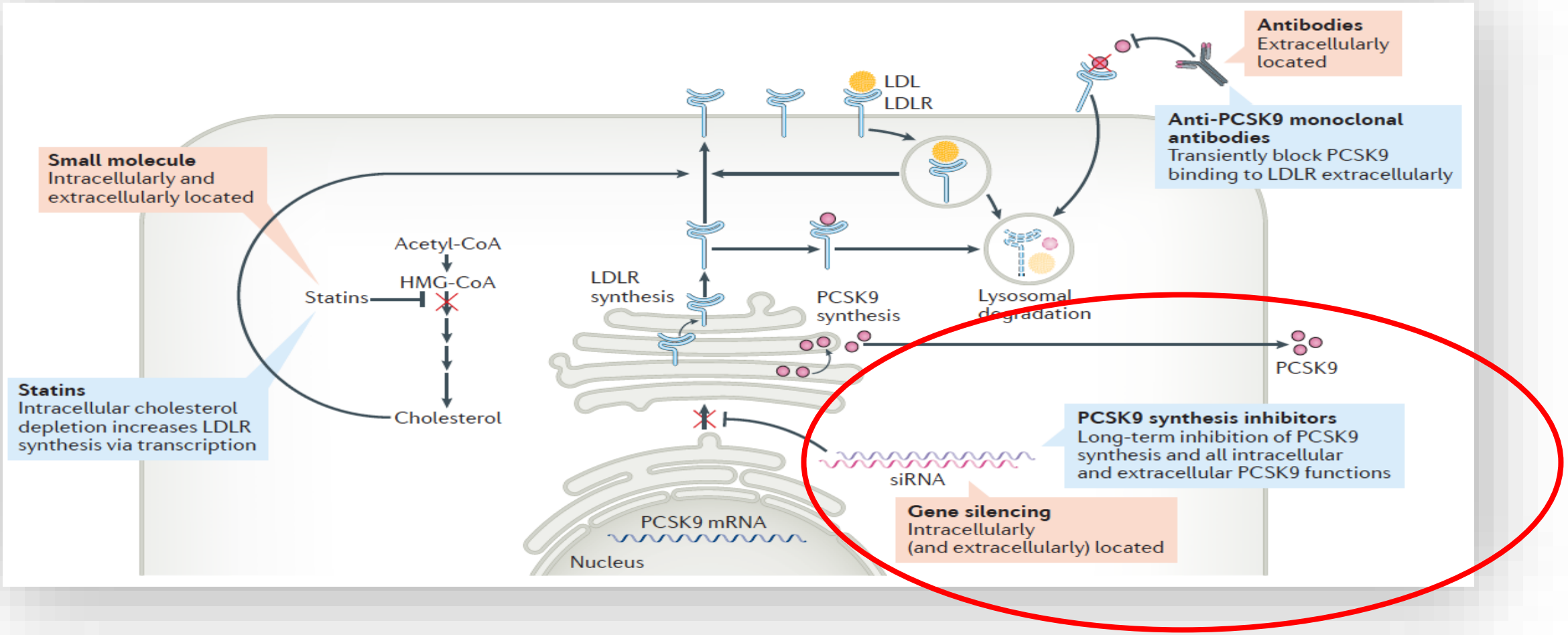


Fully human monoclonal antibody against PCSK9 inhibits PCSK9/LDL-R interaction



PNAS 2009;106:9820

Approaches to reduce LDL-C levels



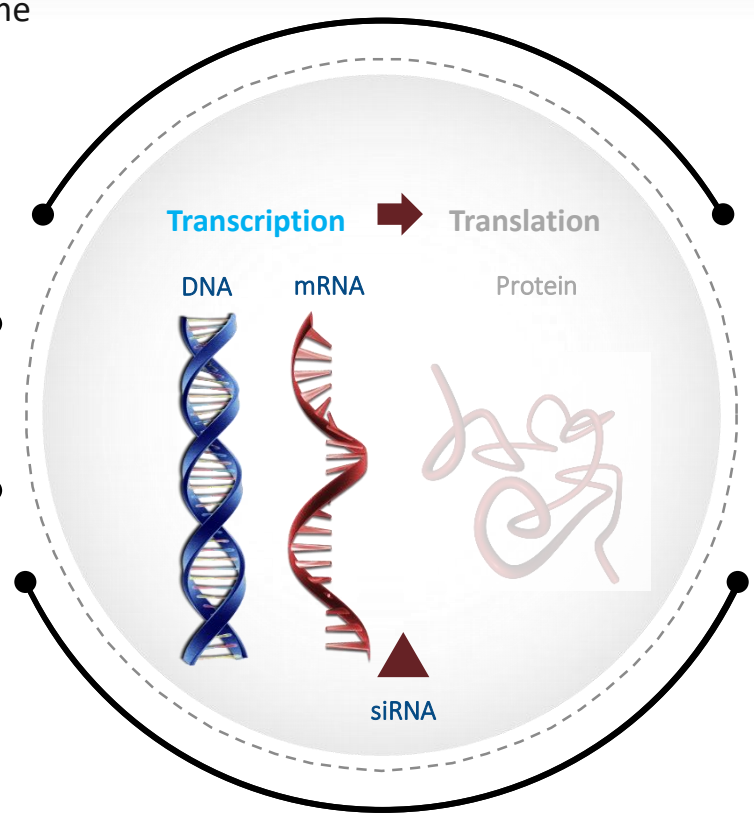
Nature Rev Cardiol 2018;15:261

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]



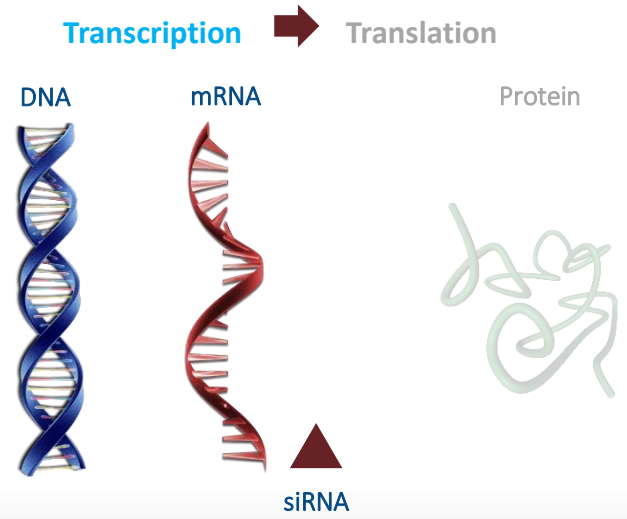
ncRNAs are involved in **gene regulation**, RNA maturation and protein synthesis[1]

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]

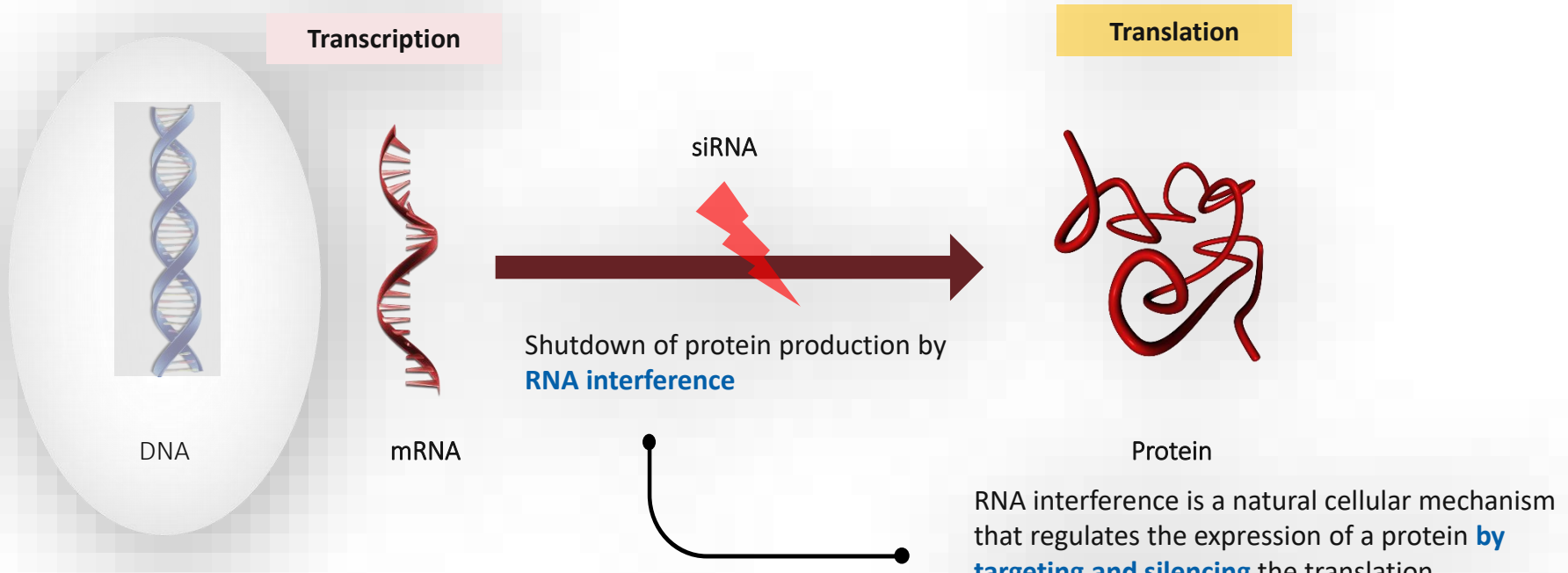
RNAi therapeutics harness the natural biologic pathway of RNAi to regulate expression of specific genes[2]

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 ?

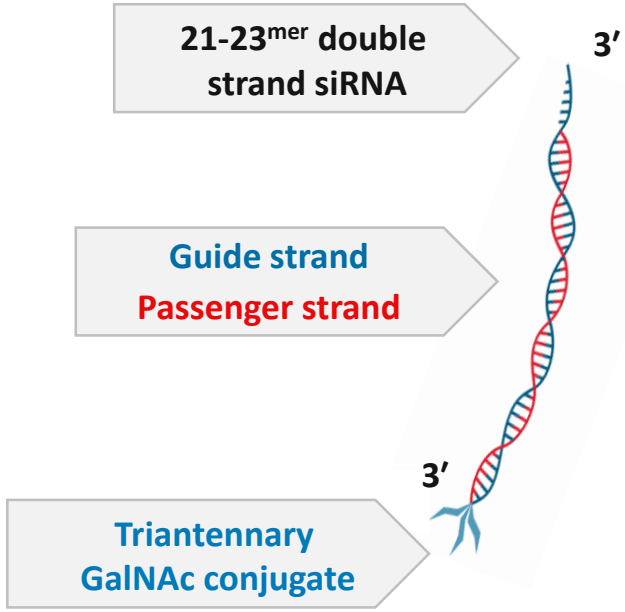
Small interfering RNA

- 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**

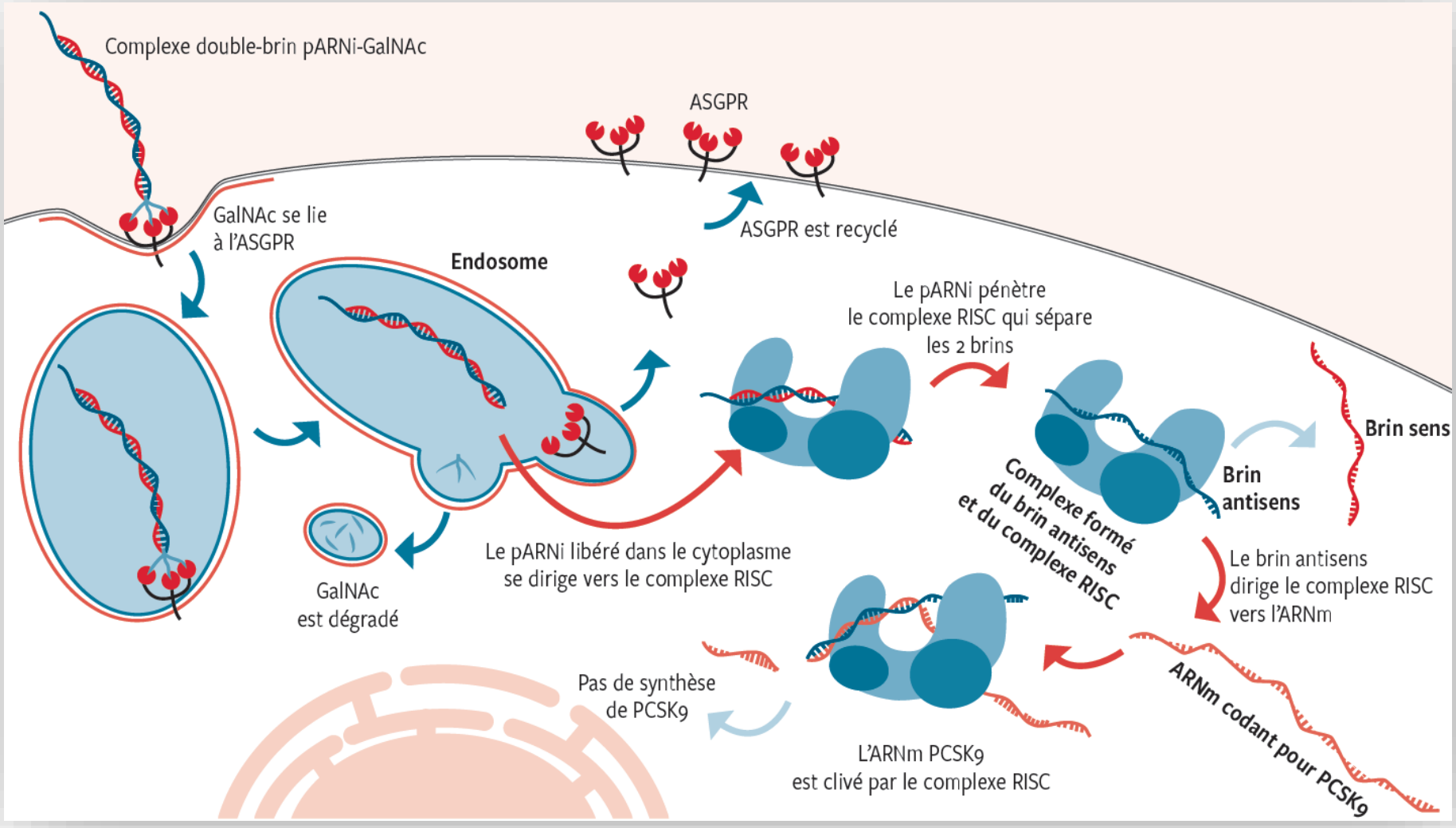
Inclisiran



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

Mechanism of action

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



Rev Med Suisse 26 mai 2021;740:xxx

Inclisiran treatment

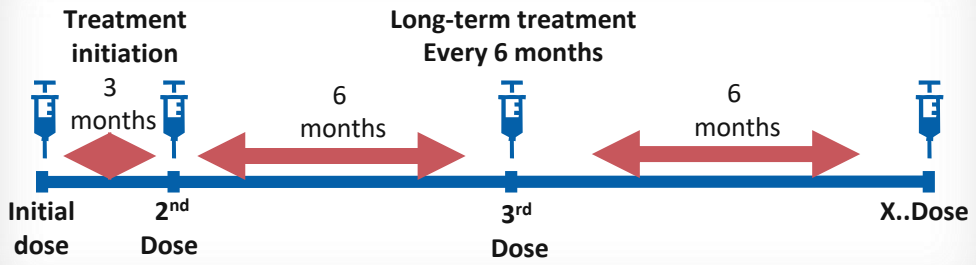
Dose & administration

Injection[1,2]

1.5 mL solution per syringe

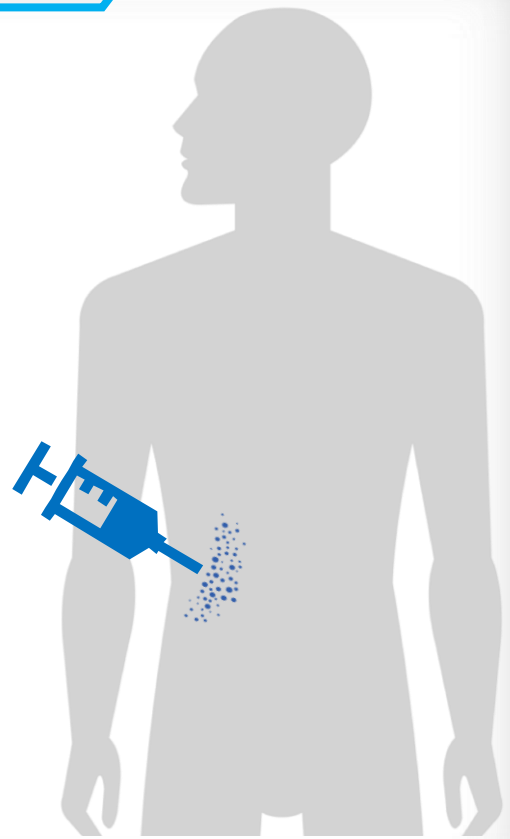
- 300 mg inclisiran sodium*
- Water as the diluent
- Sodium hydroxide and phosphoric acid (pH 7)
- Stored at room temperature

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]
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ORION-12	I	48	Population saine	180 jours	QT et ECG	–
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ORION-15	II	308	Étude de recherche de dose, ASCVD	270 jours	Baisse du LDL-C	NCT04666298
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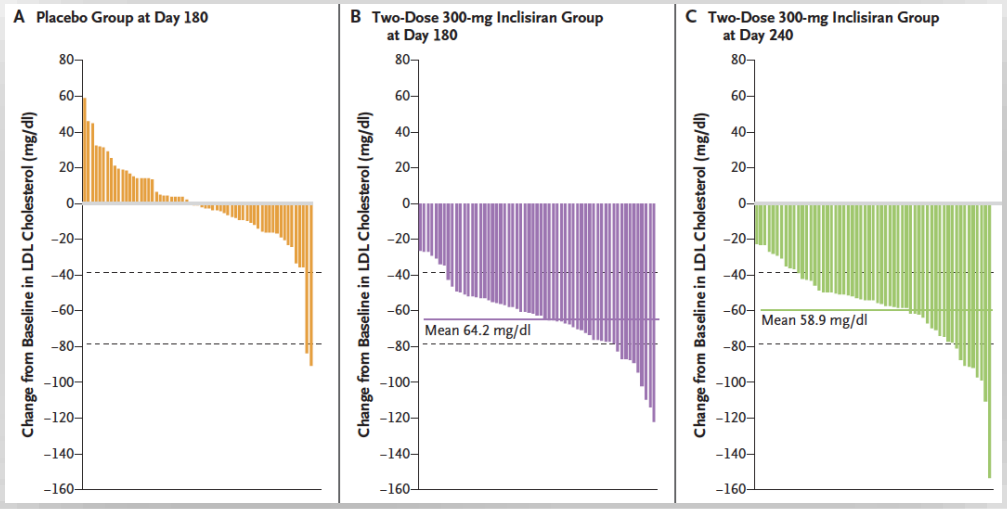
Lowering PCSK9 with siPCSK9

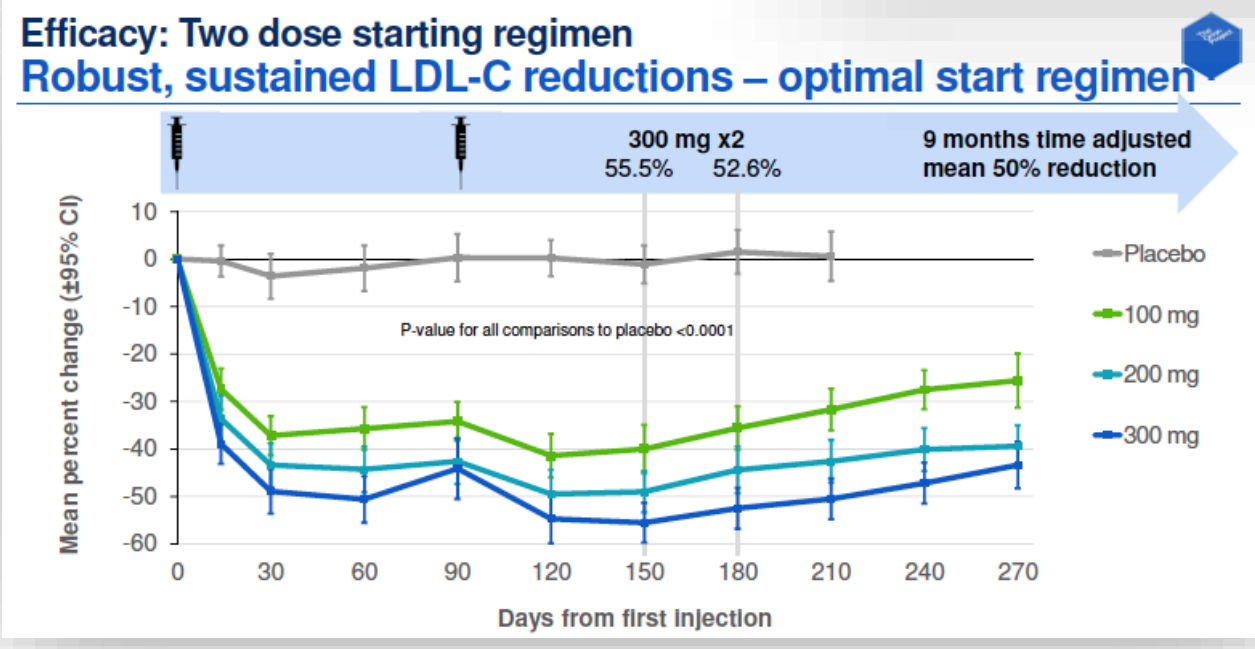
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

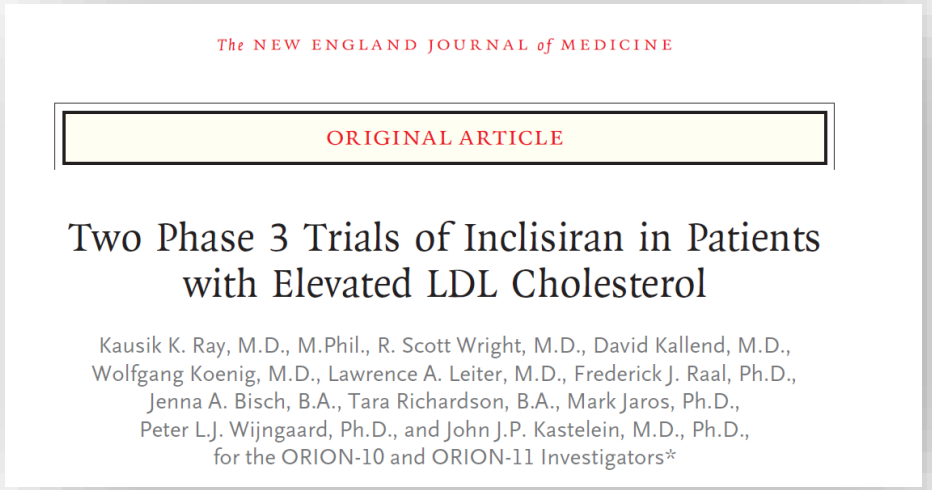
Kausik K. Ray, M.D., Ulf Landmesser, M.D., Lawrence A. Leiter, M.D., David Kallend, M.D., Robert Dufour, M.D., Mahir Karakas, M.D., Tim Hall, M.D., Roland P.T. Troquay, M.D., Traci Turner, M.D., Frank L.J. Visseren, M.D., Peter Wijngaard, Ph.D., R. Scott Wright, M.D., and John J.P. Kastelein, M.D., Ph.D.





New Engl J Med 2017;376:1430

Lowering PCSK9 with siPCSK9



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*

Efficacy and safety of Inclisiran vs placebo

in patients with very high cardiovascular risk,

with ASCVD or ASCVD-Risk Equivalent *

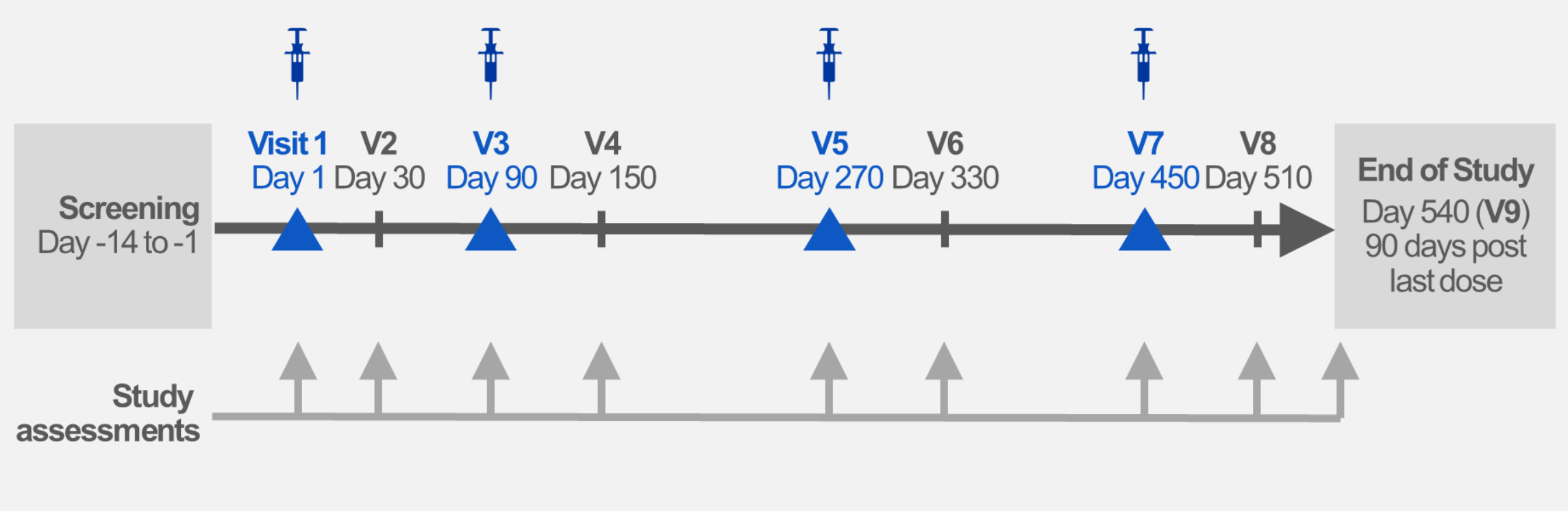
*Type-2 Diabetes, familial hypercholestereolemia or 10-year risk ≥20%

New Engl J Med 2020;382:1507

ORION-11: Study design

Eighteen months treatment and observation

Randomized 1:1 inclisiran 300 mg vs. placebo – with maximally tolerated statins

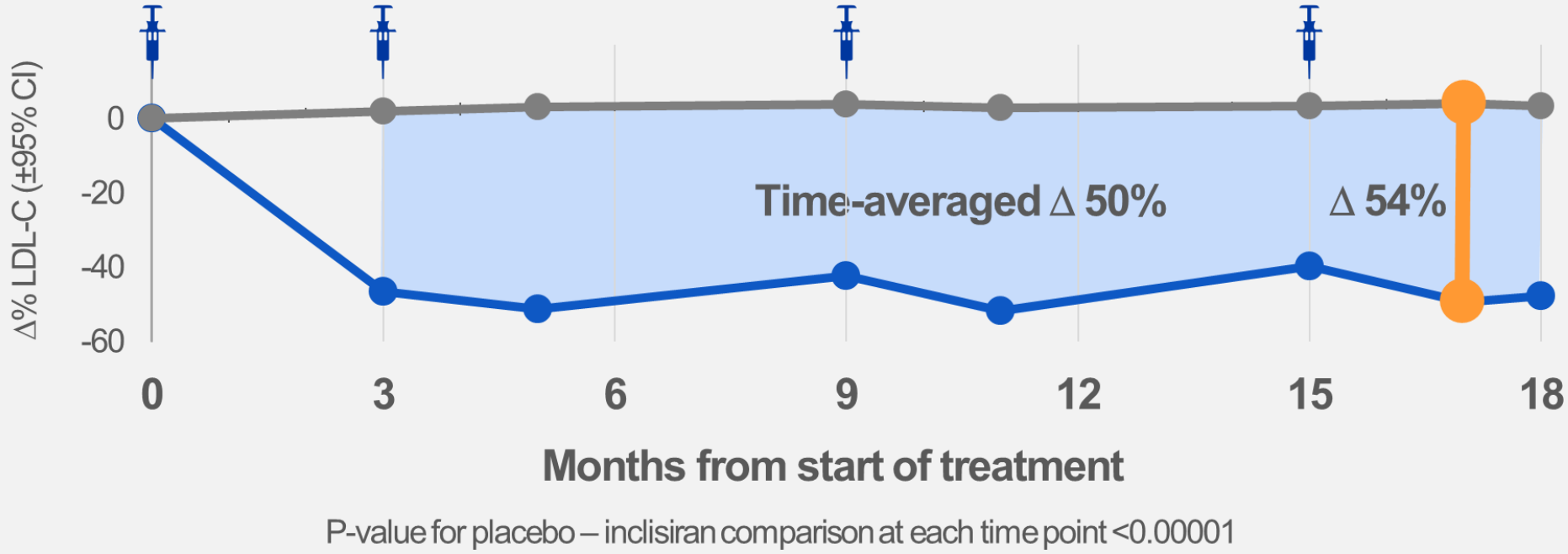


New Engl J Med 2020;382:1507

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

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

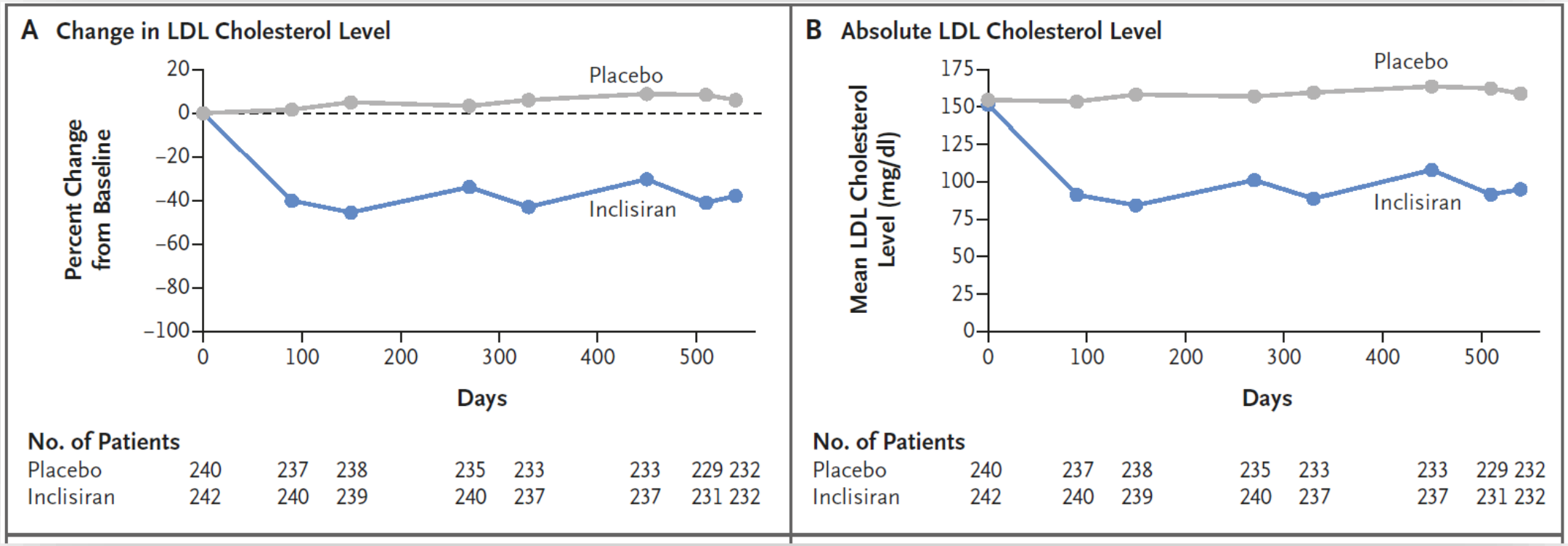


1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

New Engl J Med 2020;382:1507

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

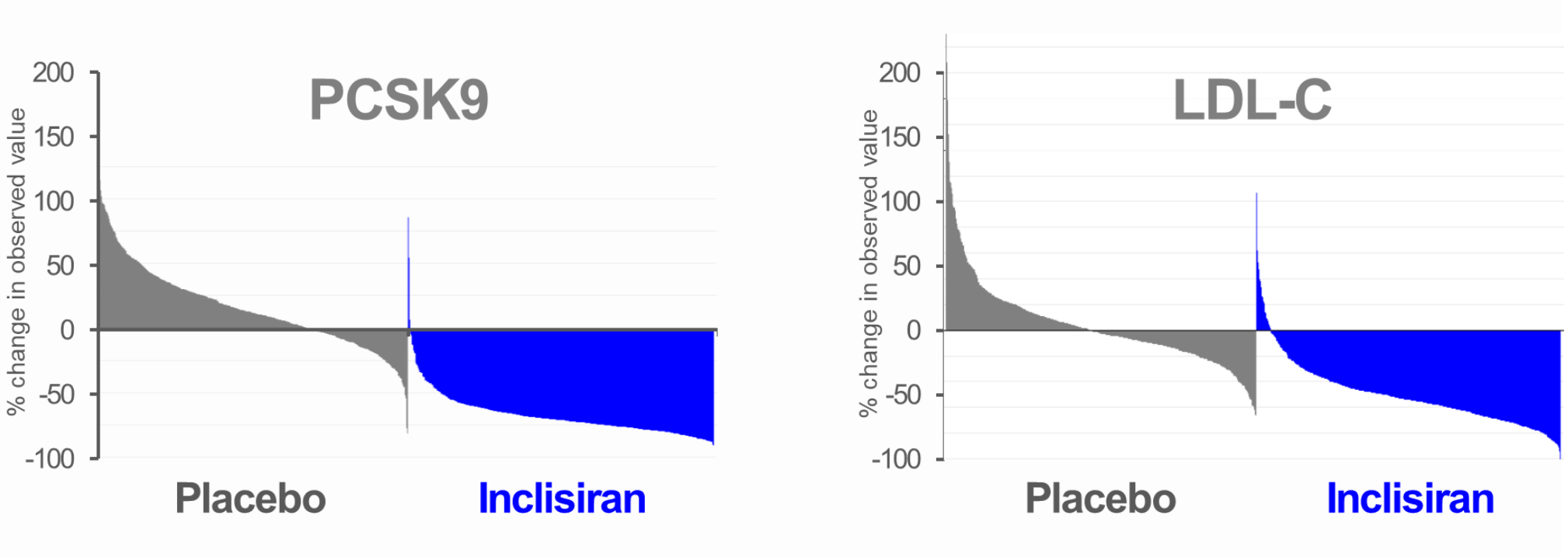


New Engl J Med 2020;382:1507

ORION-11: Efficacy

Potent, consistent response to inclisiran

Individual patient responses contributing to primary endpoint – 17 months

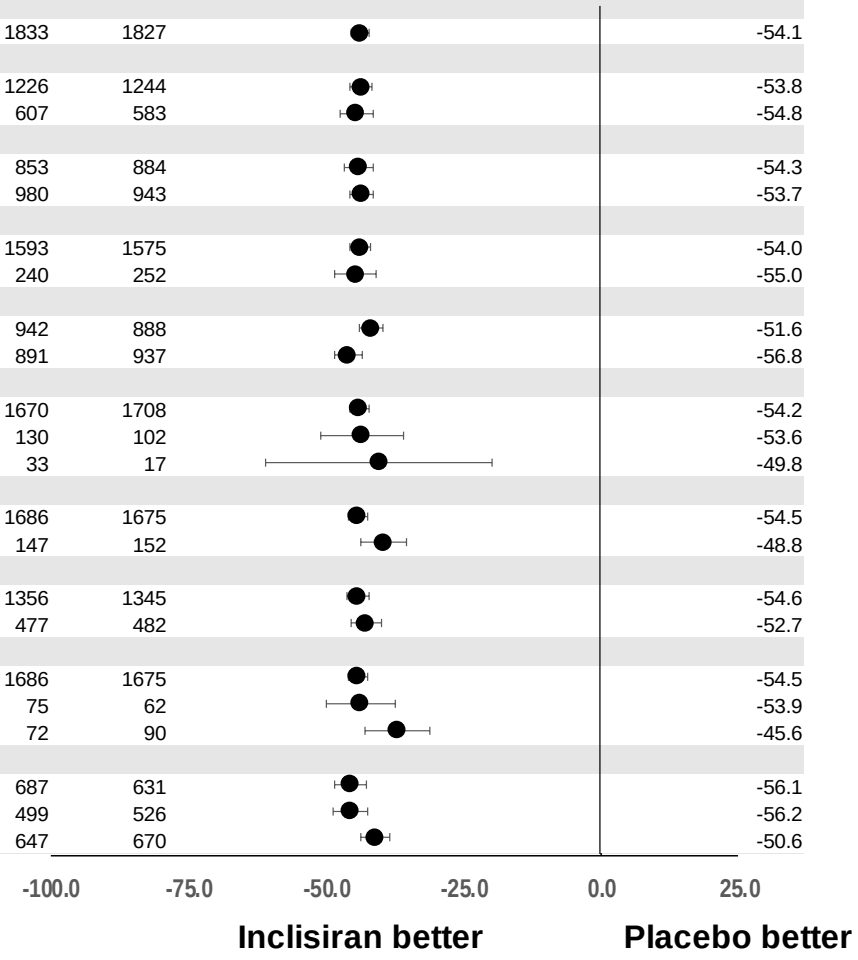


New Engl J Med 2020;382:1507

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

ORION-11: Safety and tolerability

No difference in serious adverse events

Serious TEAEs	Placebo		Inclisiran	
Safety population[1,2]	N = 804		N = 811	
Patients with at least one serious TEAE	181	(22.5%)	181	(22.3%)
All cause death	15	(1.9%)	14	(1.7%)
Cardiovascular	10	(1.2%)	9	(1.1%)
Cancer	3	(0.4%)	3	(0.4%)
New, worsening or recurrent malignancy	20	(2.5%)	16	(2.0%)

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

New Engl J Med 2020;382:1507

ORION-11: Exploratory endpoint

Adverse cardiovascular events

Cardiovascular TEAEs	Placebo		Inclisiran	
Safety population[1,2]	N = 804		N = 811	
Pre-specified exploratory CV endpoint[3]	83	(10.3%)	63	(7.8%)
Cardiovascular death	10	(1.2%)	9	(1.1%)
Fatal or non-fatal MI and stroke[4]	30	(3.7%)	12	(1.5%)
Fatal or non-fatal MI	22	(2.7%)	10	(1.2%)
Fatal or non-fatal stroke	8	(1.0%)	2	(0.2%)

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. MedDRA-defined CV basket of non-adjudicated terms cardiac death, and any signs of cardiac arrest, non-fatal MI and/or stroke
4. Post-hoc analysis of hard endpoints

New Engl J Med 2020;382:1507

ORION-11: Summary

Twice-a-year inclisiran lowered LDL-C by ≥50% safely

Efficacy

- ORION-11 met all primary and secondary endpoints
- Inclisiran reduced the primary LDL-C endpoint by 54% at 17 months, 50% time averaged
- Inclisiran resulted in potent, consistent PCSK9 knock down

Safety and tolerability

- Inclisiran safety profile was similar to placebo
- No adverse changes in laboratory markers
- Injection site events 4.2% - predominantly mild and none persistent

Exploratory endpoint

- Numerically fewer CV events were reported for inclisiran than placebo

New Engl J Med 2020;382:1507

ORION-11: Conclusions and implications

Inclisiran is the first cholesterol lowering siRNA

Inclisiran achieves durable and potent LDL-C reduction with only 2x yearly injection

Excellent safety profile in a high cardiovascular risk population

Administration by HCP potentially coincides with typical six-monthly patient visits

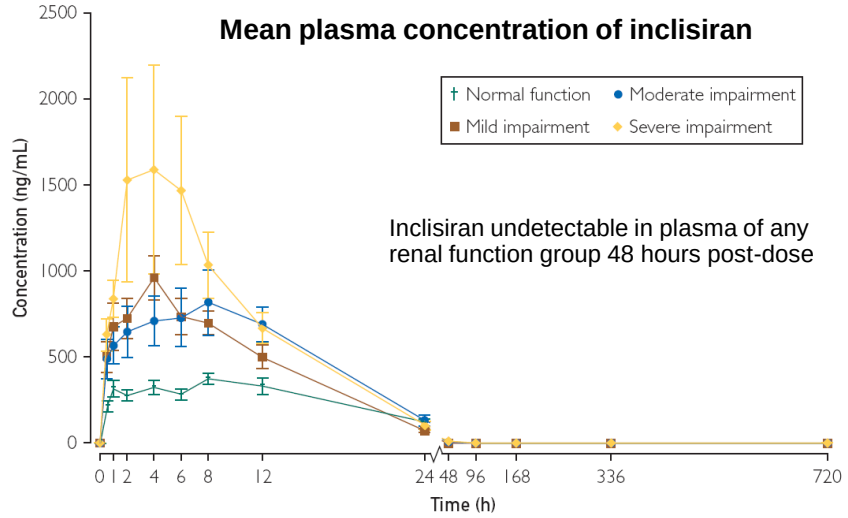
- Lends itself to routine clinical practice
- Enables provider control over medication adherence
- May offer patients meaningful new choices
- Offering safe, convenient and assured results

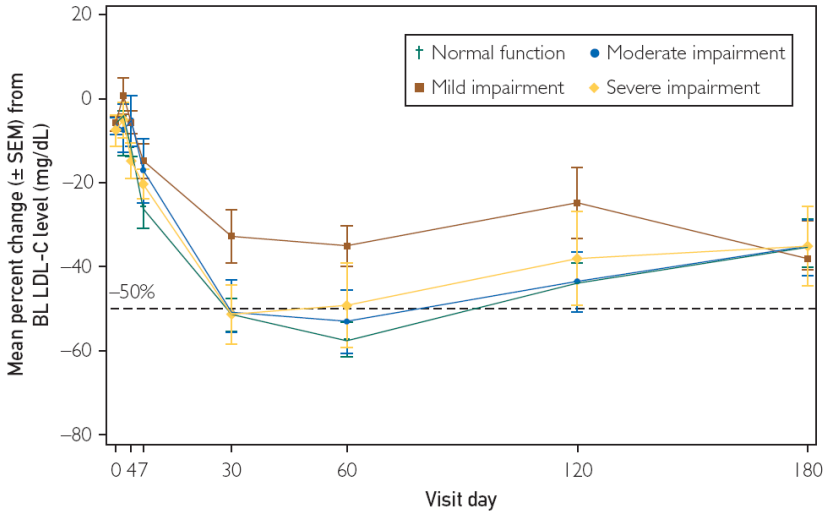
New Engl J Med 2020;382:1507

ORION-17: Renal impairment study

Dose adjustments unnecessary for impaired renal function

Single 300-mg dose, open-label study in subjects with various levels of renal function (n=31)





Inclisiran safety and tolerability were unaffected by renal impairment

Mayo Clin Proc 2020;95:77

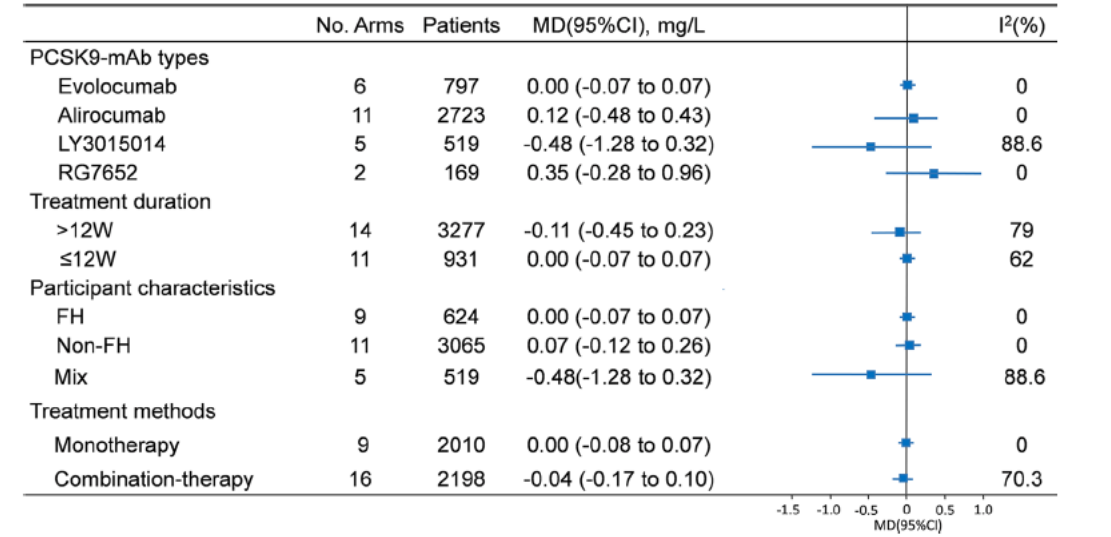
PCSK9i and C-Reactive Protein

Open access Research

BMJ Open

Impact of PCSK9 monoclonal antibodies on circulating hs-CRP levels: a systematic review and meta-analysis of randomised controlled trials

Ye-Xuan Cao, Sha Li, Hui-Hui Liu, Jian-Jun Li



	No. Arms	Patients	MD(95%CI), mg/L	I^2(%)
PCSK9-mAb types				
Evolocumab	6	797	0.00 (-0.07 to 0.07)	0
Alirocumab	11	2723	0.12 (-0.48 to 0.43)	0
LY3015014	5	519	-0.48 (-1.28 to 0.32)	88.6
RG7652	2	169	0.35 (-0.28 to 0.96)	0
Treatment duration				
>12W	14	3277	-0.11 (-0.45 to 0.23)	79
≤12W	11	931	0.00 (-0.07 to 0.07)	62
Participant characteristics				
FH	9	624	0.00 (-0.07 to 0.07)	0
Non-FH	11	3065	0.07 (-0.12 to 0.26)	0
Mix	5	519	-0.48(-1.28 to 0.32)	88.6
Treatment methods				
Monotherapy	9	2010	0.00 (-0.08 to 0.07)	0
Combination-therapy	16	2198	-0.04 (-0.17 to 0.10)	70.3

BMJ 2018;e022348

Am J Cardiovasc Drugs (2018) 18:271–282
https://doi.org/10.1007/s40256-018-0270-7

SYSTEMATIC REVIEW

Comparative Effectiveness of Inclisiran 100, 300, and 500 mg in a Population with Hyperlipidemia: A Network Meta-Analysis of Randomized Controlled Trials

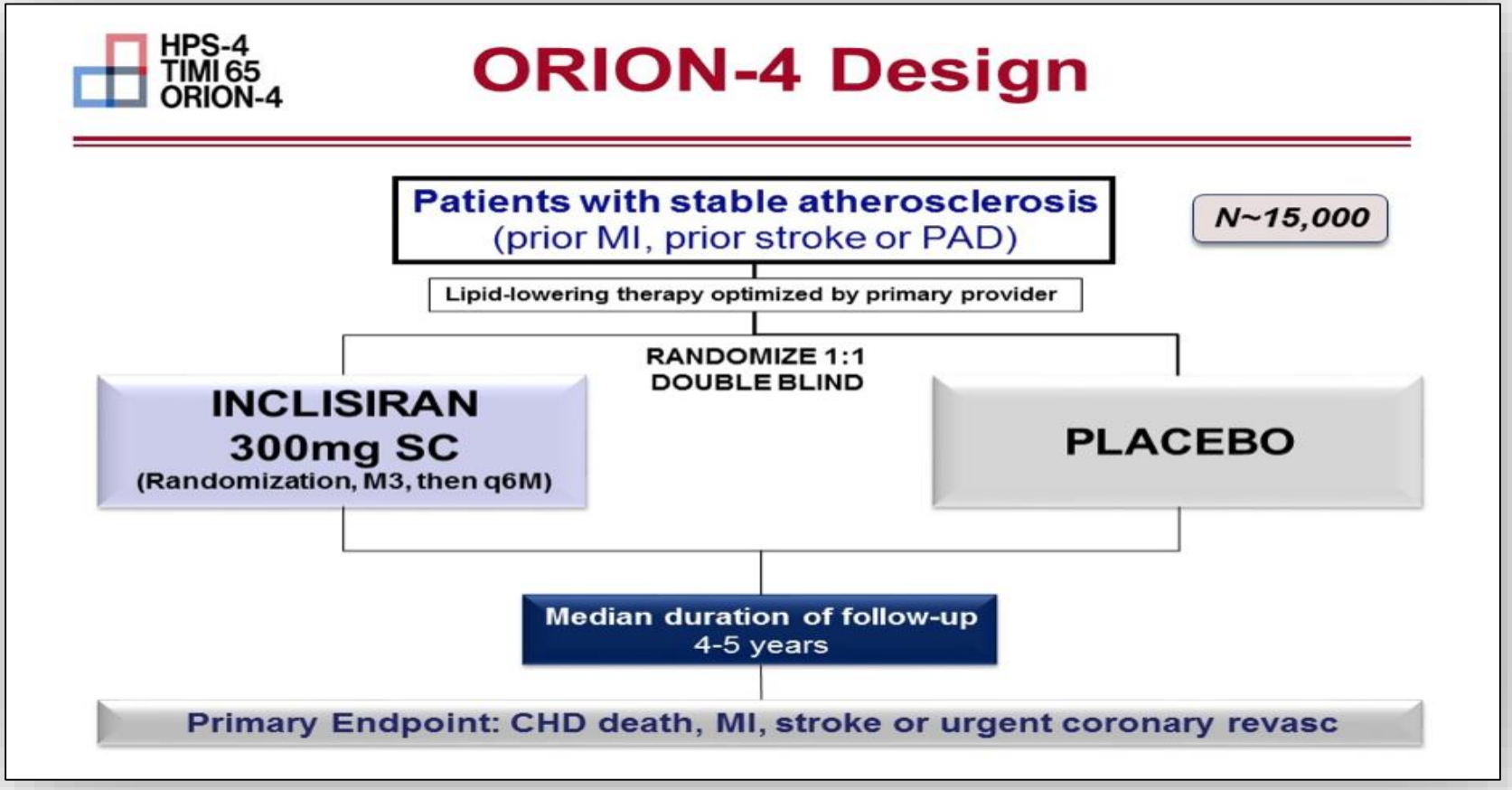
Yang Wang[1] · Jinsong Wang[1] · Shenming Wang[1]

The most commonly reported adverse events were musculoskeletal pain, nasopharyngitis, headache, and elevated C-reactive protein (CRP), none of which were significant ($p > 0.05$).

Am J Cardiovasc Drugs 2018;18:271

Opportunities and challenges for the future

Efficacy of different approaches to lipid lowering



Inclisiran / Leqvio®

Indications cliniques

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4. INFORMATIONS CLINIQUES

4.1 Indications thérapeutiques

Leqvio est indiqué chez l'adulte présentant une hypercholestérolémie primaire (hétérozygote familiale et non familiale) ou une dyslipidémie mixte, en complément d'un régime alimentaire :

- en association avec une statine seule ou une statine avec d'autres thérapies hypolipémiantes chez les patients ne pouvant atteindre les objectifs de LDL-C sous statine à dose maximale tolérée, ou
- seul ou en association avec d'autres thérapies hypolipémiantes chez les patients intolérants aux statines, ou chez qui les statines sont contre-indiquées.

4.2 Posologie et mode d'administration

Posologie

La dose recommandée est de 284 mg d'inclisiran administrée en une seule injection sous-cutanée : une première fois, puis à 3 mois, puis tous les 6 mois.

https://www.ema.europa.eu/en/documents/product-information/leqvio-epar-product-information_fr.pdf

Inclisiran clinical studies

ORION development program

2 premières injections suisses début mai 2021

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ORION-9	III	482	HFHe	18 mois	Baisse du LDL-C	NCT03814187
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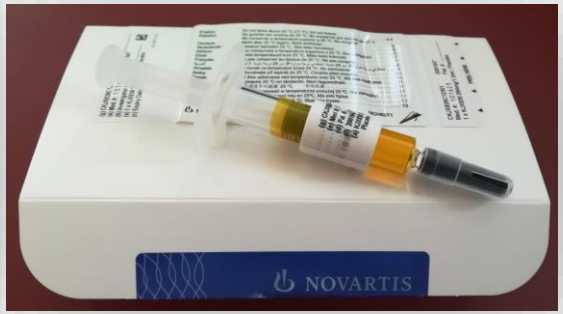


The modern concept of lipid-lowering strategies to reduce cardiovascular diseases

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

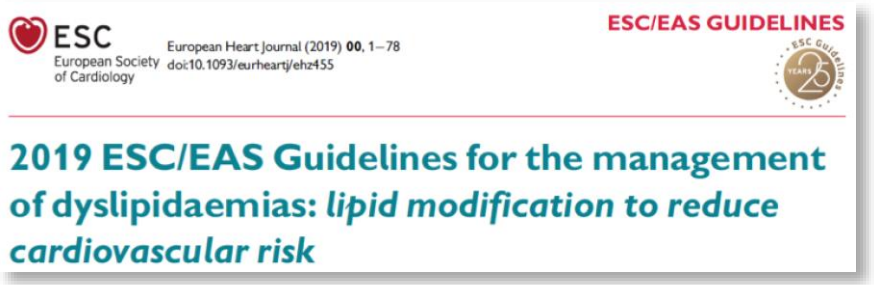
Pr FRANÇOIS MACH et Pr OLIVIER MULLER

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:xxx

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



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"

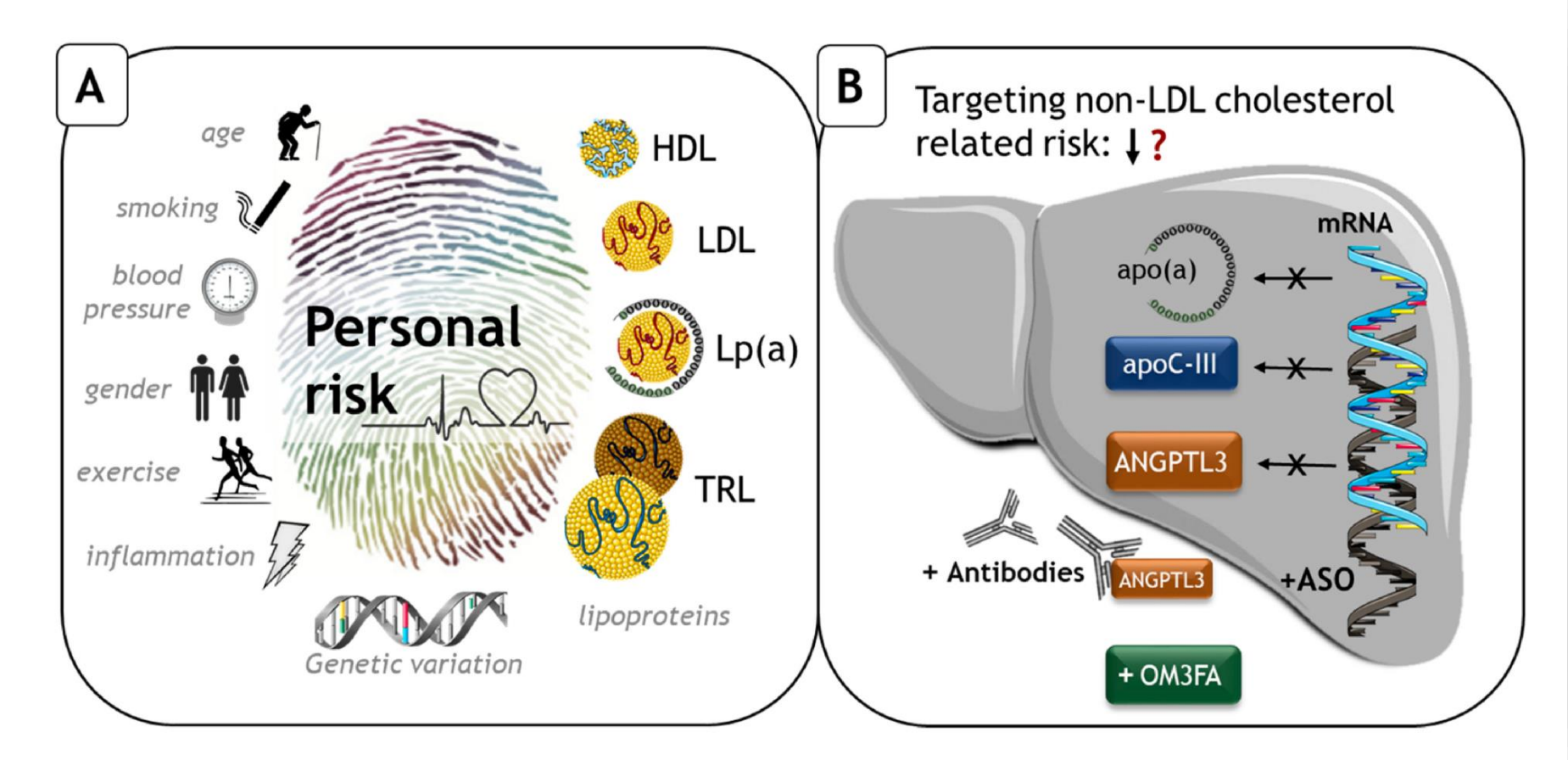
Concept change III: Use lipid-lowering combination therapy

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

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

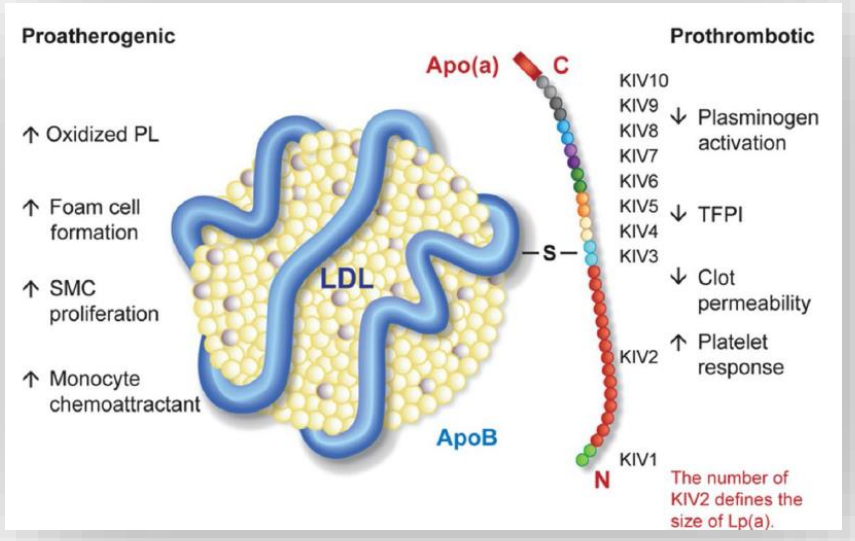
Statin +/- ezetimibe + siRNA induced LDL-C lowering with great efficacy, safety and full treatment's adherence

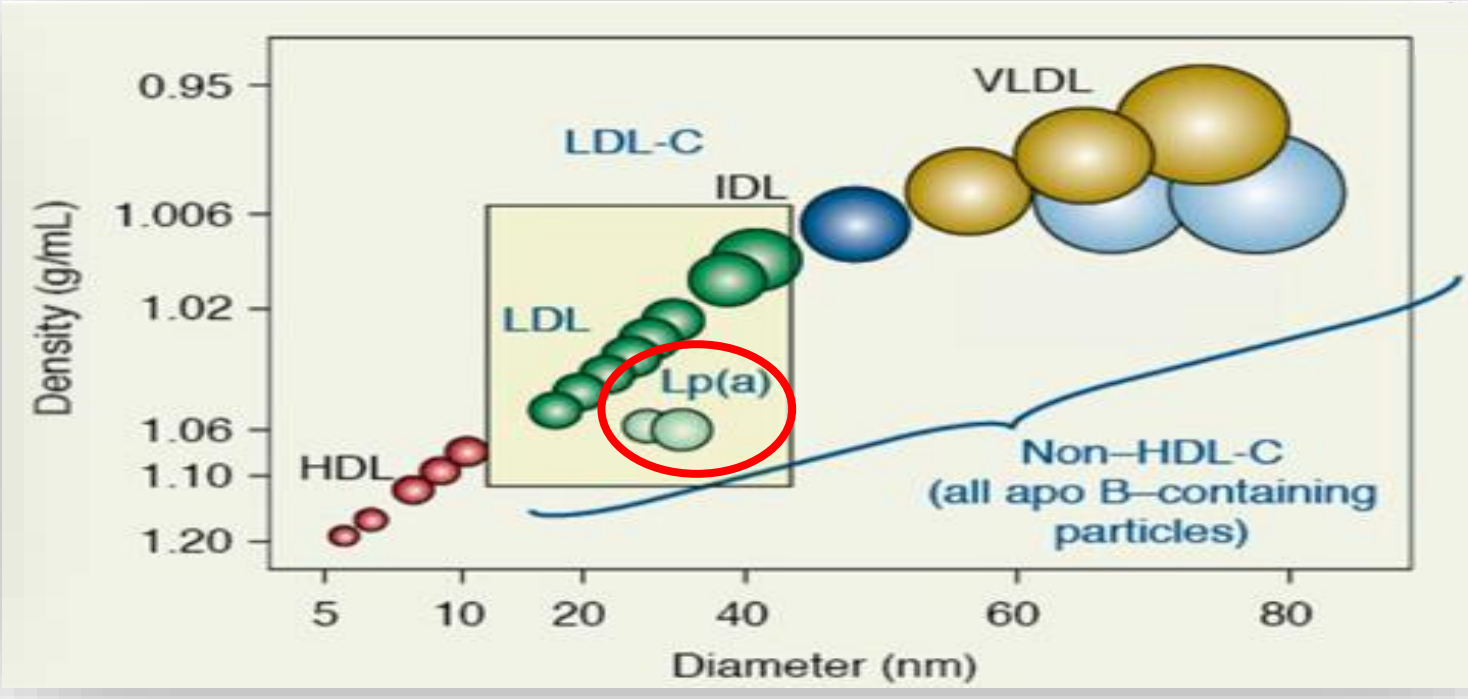
Novel lipid lowering drugs: PCSK9 and beyond



Clin Med. 2019;8:1085

Characteristics of lipoproteins





Lipoprotein(a)

Lipoprotein(a) is a CV risk factor

European Heart Journal (2017) **0**, 1–8
doi:10.1093/eurheartj/ehx033

REVIEW

Frontiers in Cardiovascular Medicine

Lipoprotein(a): the revenant

Baris Gencer[1], Florian Kronenberg[2], Erik S. Stroes[3], and François Mach[1]*

[1]Cardiology Division, Geneva University Hospitals, Switzerland; [2]Department of Medical Genetics, Division of Genetic Epidemiology, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Austria; and [3]Academic Medical Center, Amsterdam, AZ 1100, The Netherlands

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 2597–2599
doi:10.1093/eurheartj/ehy385

EDITORIAL

Lipoprotein(a): the perpetual supporting actor

Baris Gencer and François Mach*

Cardiology Division, Department of Specialties in Medicine, Geneva University Hospitals, Rue Gabrielle-Perret Gentil 4, 1211 Geneva 14, Switzerland

Drugs
https://doi.org/10.1007/s40265-019-01243-5

REVIEW ARTICLE

Potential of Lipoprotein(a)-Lowering Strategies in Treating Coronary Artery Disease

Baris Gencer[1,2] · François Mach[1]

Key Points

High levels of lipoprotein(a) are considered causal risk factor of cardiovascular disease (CVD).

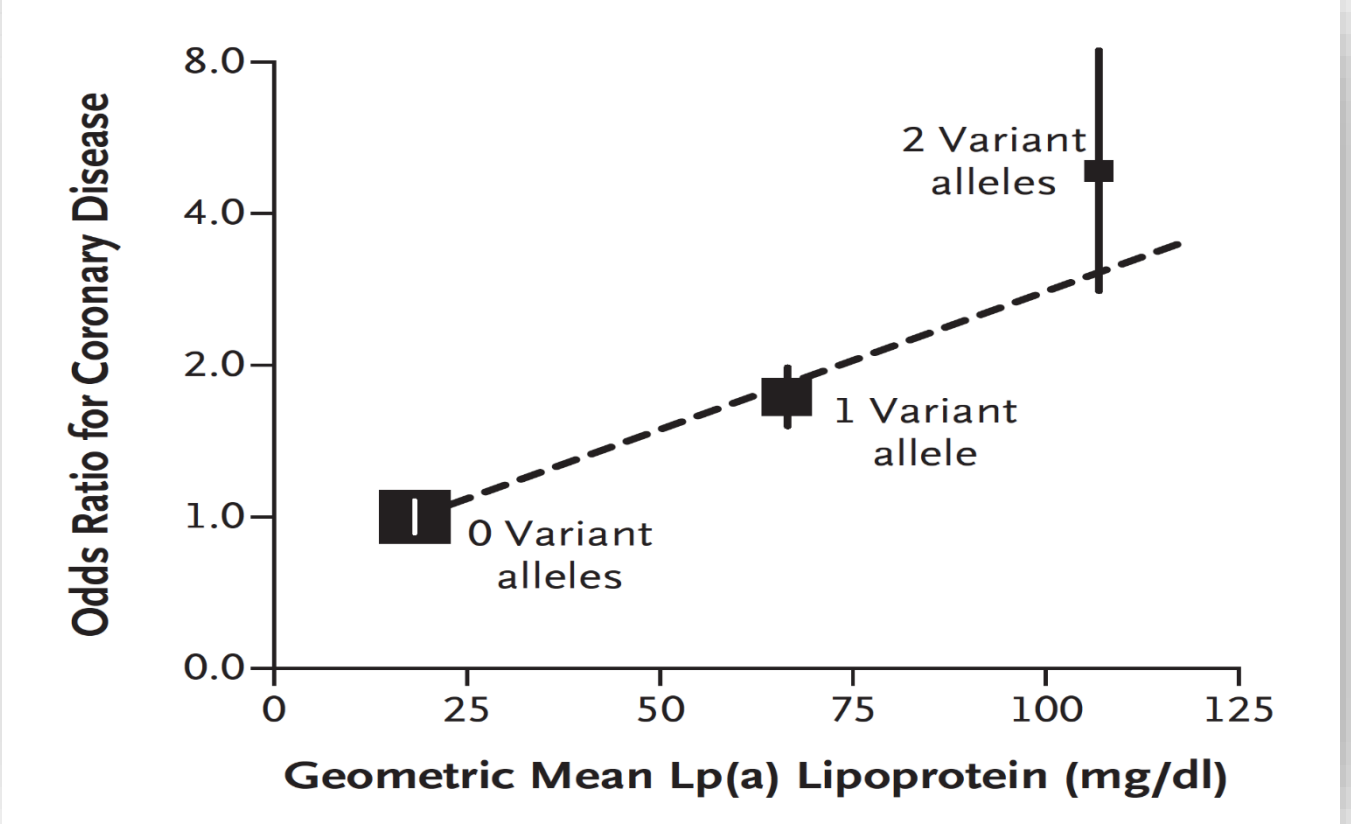
The 2019 ESC/EAS guidelines for the management of dyslipidaemia recommend to measure Lp(a) at least once in each adult person's lifetime.

To lower Lp(a), two antisense oligonucleotides are under development, targeting apolipoprotein (B) and apolipoprotein (a).

Lipoprotein(a) and CV risk

ORIGINAL ARTICLE

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



New Engl J Med 2009;361:2518

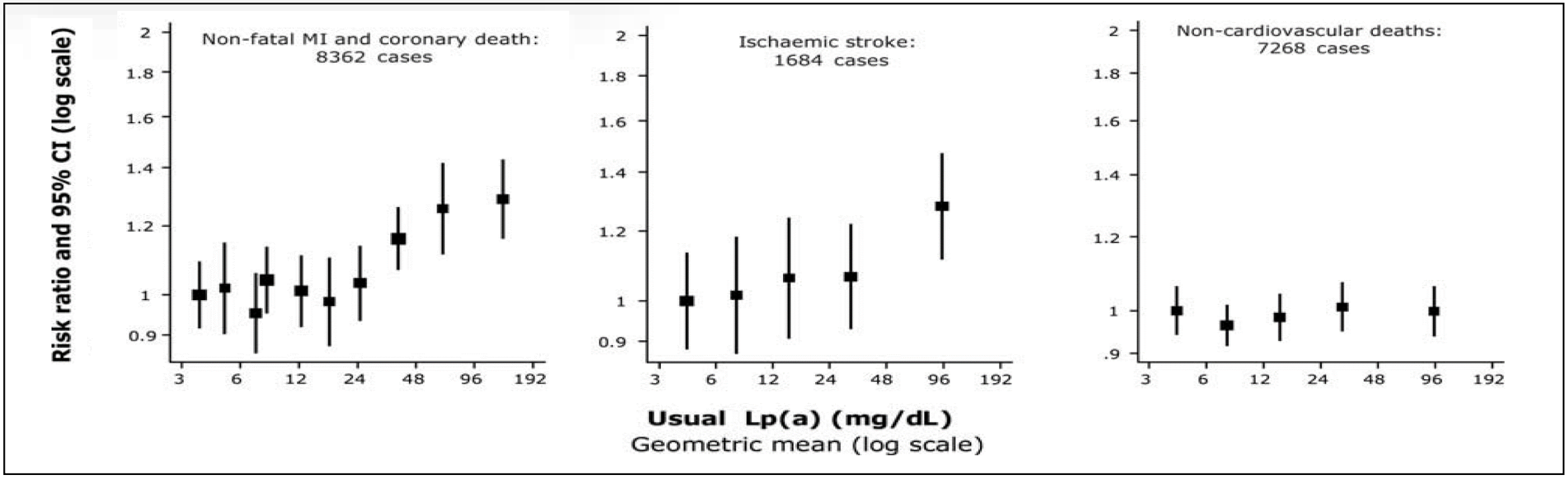
Lipoprotein(a) and CV risk

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

CURRENT OPINION

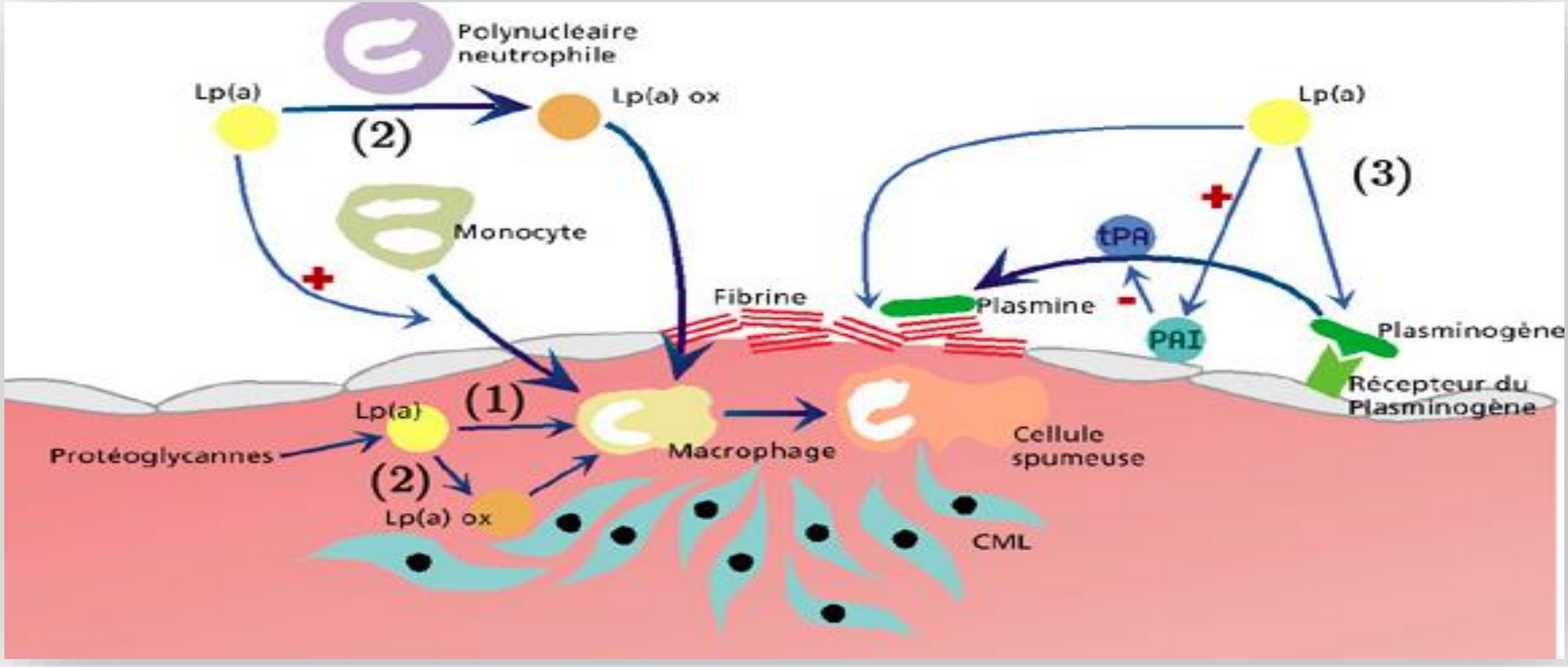
Lipoprotein(a) as a cardiovascular risk factor: current status

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

Lipoprotein(a) – The perfect killer



Recommendations for lipid analysis

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)

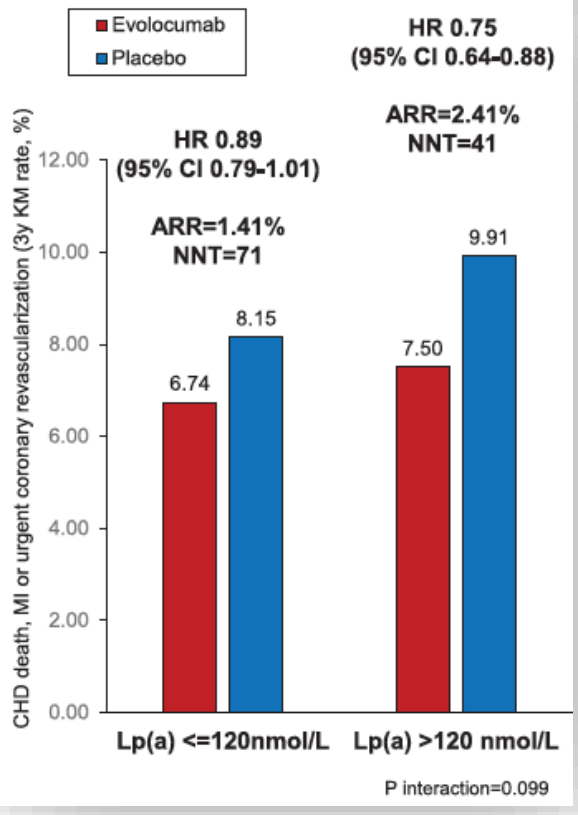
PCSK9 mAb - Lp(a) and CV outcomes ?

Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

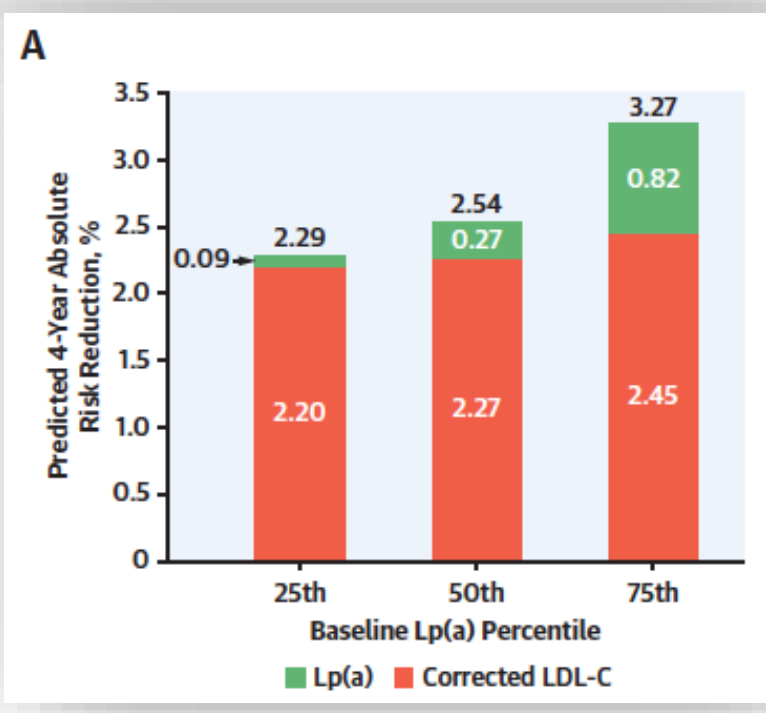
Insights From the FOURIER Trial



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

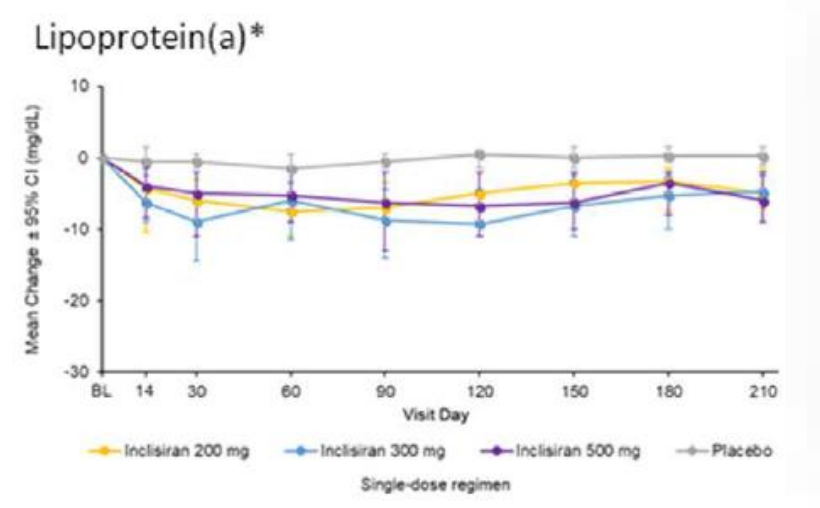


Table 2. Lipids and Lipoproteins at Baseline and Day 180*

	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

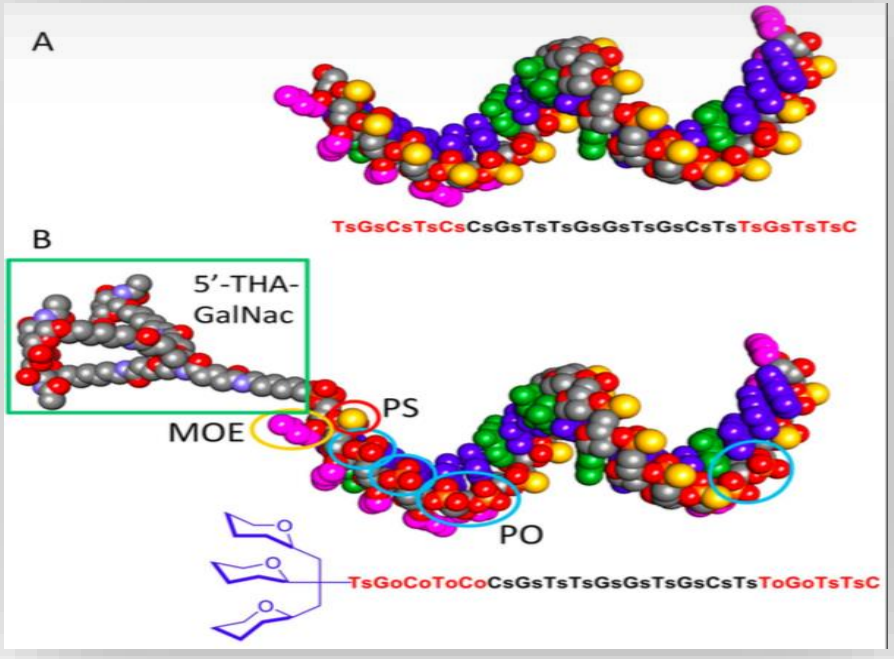
Lowering Lipoprotein(a) with apo(a)-antisense

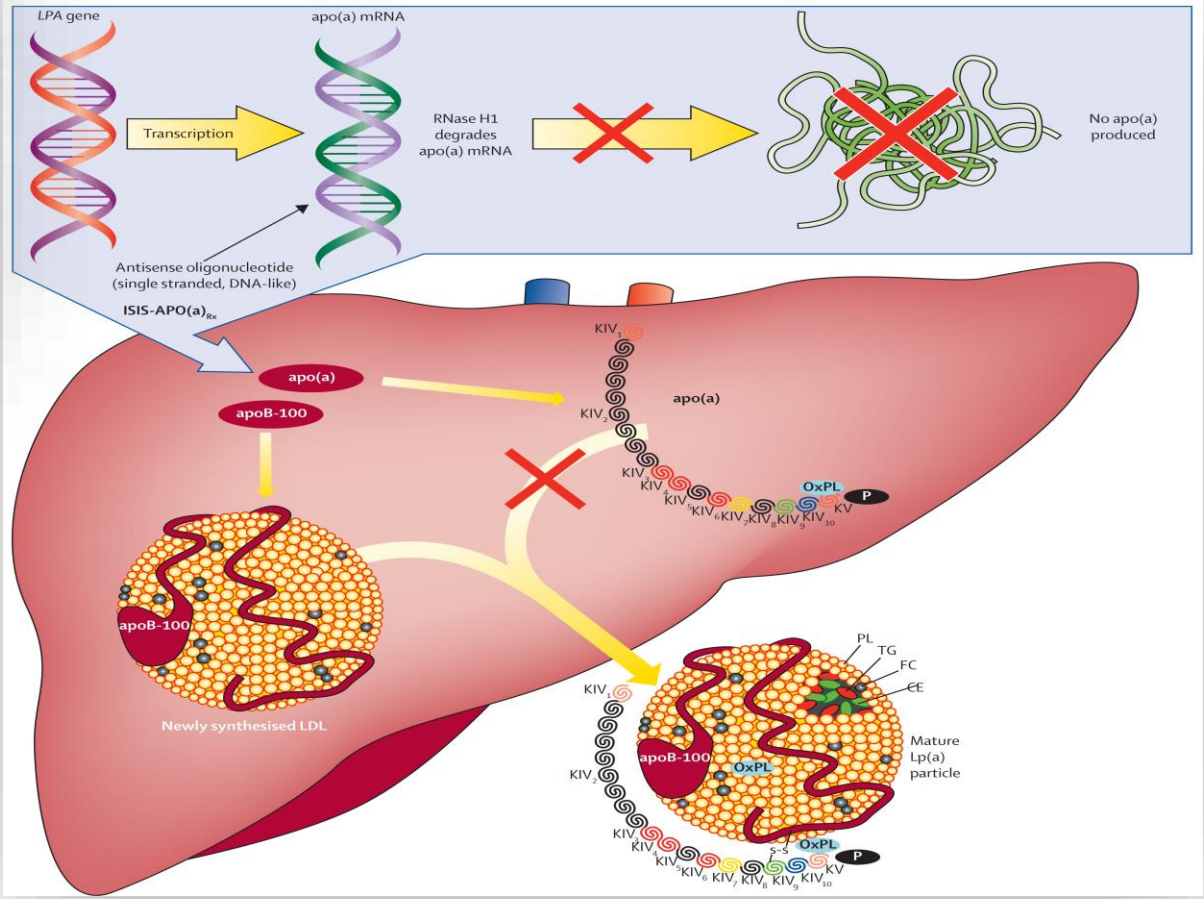
Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

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

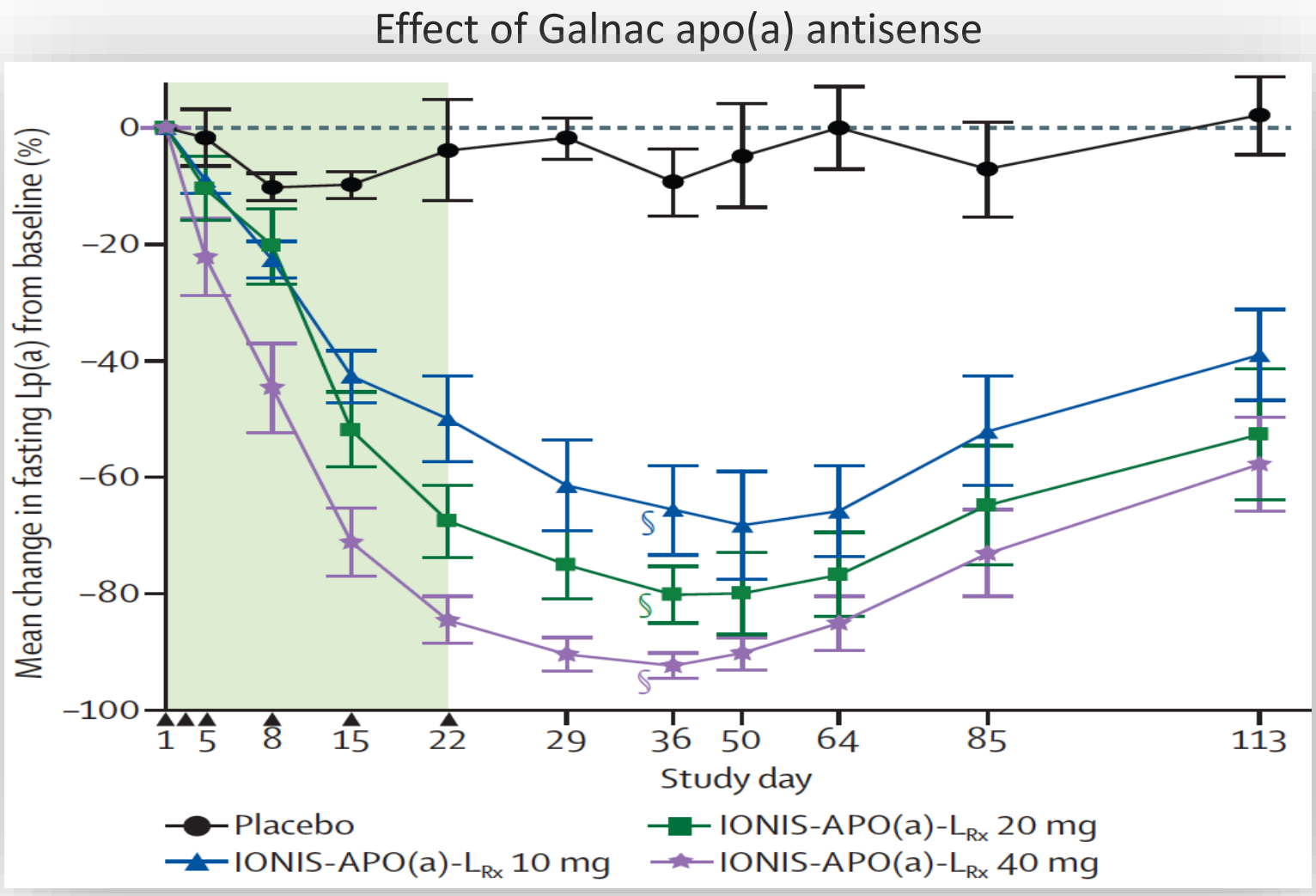
Nicholas J Viney, Julian C van Capelleveen, Richard S Geary, Shuting Xia, Joseph A Tami, Rosie Z Yu, Santica M Marcovina, Steven G Hughes, Mark J Graham, Rosanne M Crooke, Stanley T Crooke, Joseph L Witztum, Erik S Stroes, Sotirios Tsimikas





Lancet 2015;386:1472

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



Lancet 2016;388:2239

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

P2338

Safety, Tolerability, and Efficacy of Single-dose AMG 890, a Novel siRNA Targeting Lp(a), in Healthy Subjects and Subjects With Elevated Lp(a)

Michael J Koren,[1] Patrick Maurice Moriarty,[2] Joel Neutel,[3] Seth J Baum,[4*] Martha Hernandez-Illas,[5] Howard S Weintraub,[6] Jennifer Hellawell,[7] Tracy Varrieur,[8] Winnie Sohn,[9] Huei Wang,[10] Mary Elliott-Davey,[11] Helina Kassahun,[9] Gerald F Watts[12†]

[1]Jacksonville Center for Clinical Research, Jacksonville, FL; [2]University of Kansas Medical Center, Kansas City, KS; [3]Orange County Research Center, Tustin, CA; [4]Preventive Cardiology Inc, Boca Raton, FL; [5]OPS MRA, Miami, FL; [6]NYU Langone Medical Center, New York, NY; [7]Amgen, South San Francisco, CA; [8]Amgen, Cambridge, MA; [9]Amgen, Thousand Oaks, CA; [10]Amgen, Newbury Park, CA; [11]Amgen Ltd, Cambridge; [12]University of Western Australia, Perth, Australia

*Current affiliation: Baum Medical Clinical Trials, Boca Raton, FL, USA.
†Current affiliation: School of Medicine, University of Western Australia, Department of Cardiology, Royal Perth Hospital, Perth, Australia

Background & Objective

- Lipoprotein(a) [Lp(a)] is a risk factor for myocardial infarction and other atherosclerotic events[1-3]
- No approved medicines selectively target Lp(a) and have demonstrated reduction in cardiovascular events
- Olpasiran (AMG 890) is a small interfering ribonucleic acid (siRNA) designed to reduce the production of Lp(a) by targeting messenger RNA transcribed from the *LPA* gene
- In this study (NCT 03626662), we evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of olpasiran

Methods

- Adults with plasma concentrations at screening of Lp(a) ≥70 to ≤199 nmol/L (cohorts 1–5) or ≥200 nmol/L (cohorts 6–7), were randomized 3:1 to receive a single subcutaneous dose of olpasiran or placebo (**Figure 1**)
- The primary endpoints were treatment-emergent adverse events, safety laboratory analytes, vital signs, and ECGs. Secondary endpoints included PK parameters and percent change from baseline in Lp(a)

Figure 1. Study Design

Screening was Day -28 to Day -1. ▲ = Dosing (Day 1). ♦ = End of treatment period. Subjects were to return for follow-up until Lp(a) was at least 80% of baseline (mean of screening and day 1 pre-dose values). Escalation to the next cohort occurred only after blinded assessment of safety and tolerability at each dose level after all subjects had been followed for 15 days. For cohorts 1-5 and 9, the first 2 subjects who received olpasiran and placebo (the sentinel pairs) were to be assessed for safety for at least 24 hours before completing the cohort. For cohorts 6-8, at least 5 subjects were to be on stable doses of statins for at least 6 weeks.

Disclosures & Acknowledgements

MJK: Support from Jacksonville Center for Clinical Research. **HW, MS-D, HK, JH, TV, WS:** Employees and stockholders of Amgen Inc. **GFW:** Honoraria from Amgen, Amarin/Ionis, AstraZeneca, Sanofi-Regeneron, Research grants from Amgen, Amarin/Ionis, Sanofi-Regeneron, Novartis. **PMH:** Honoraria from Esperion, Sanofi, Akcea/Ionis, CME, Innovative Biopharma, Esperion, Pfizer, Kancha, Privacy Grandeo, Piccadilly Grants from Amgen, Sanofi, FH Foundation, Kowsky, Kowa, Esperion, Genzyme, Novartis, Akcea, Regeneron, Amgen, Research/Speaker's Bureau for Amarin, Amgen, NLA. **JN, MH-I:** nothing to disclose. **SJ Baum:** Support from Sanofi, Amgen, Regeneron, Akcea, Novartis, Quidepoint Global, Gerson Lehrman Group, AstraZeneca, Speaker/Speaker's Bureau for Novo Nordisk, Boehringer Ingelheim Ltd. **HSW:** Honoraria from Amgen, Amarin, Regeneron, Research Grants from Amgen, Akcea

- This study was funded by Amgen. Ellen Stoltzfus, PhD, (Amgen Inc.) provided medical writing assistance.
- Olpasiran is an unlicensed unapproved product.

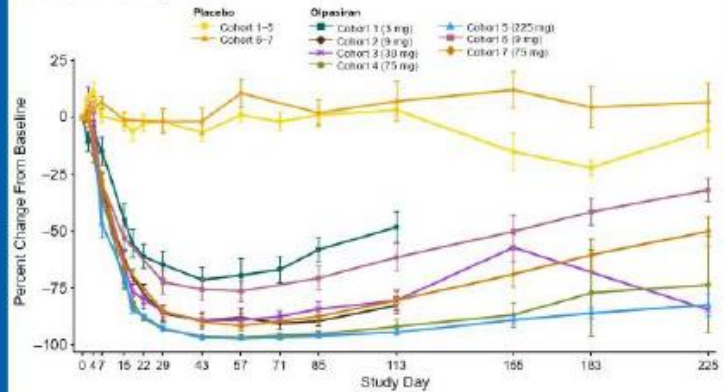
During the treatment period, one dose of olpasiran:

- **Was well tolerated**
- **Significantly reduced Lp(a) with observed approximate median percent reductions of >90% at doses ≥9 mg**
- **Led to reductions in Lp(a) persisting 3 to 6 months at doses ≥9 mg**

Table 1. Treatment-emergent Adverse Events

Adverse events, n (%)	Cohorts 1–5 Screening Lp(a) ≥70 and ≤199 nmol/L		Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L	
	Placebo (N=10)	Olpasiran (N=30)	Placebo (N=6)	Olpasiran (N=18)
Any AE	5 (50.0)	12 (40.0)	4 (66.7)	10 (55.6)
Serious AE	0	0	1 (16.7)	0
AEs occurring in more than one subject across cohorts				
Headache	1 (10.0)	0	3 (50.0)	5 (27.8)
Upper respiratory tract infection	1 (10.0)	4 (13.3)	1 (16.7)	3 (16.7)
Back pain	1 (10.0)	1 (3.3)	0	3 (16.7)
Non-cardiac chest pain	1 (10.0)	1 (3.3)	1 (16.7)	0
Viral upper respiratory tract infection	0	1 (3.3)	0	2 (11.1)
Blood creatine phosphokinase increased	1 (10.0)	1 (3.3)	0	0
Contusion	0	1 (3.3)	0	1 (5.6)
Skin abrasion	0	1 (3.3)	0	1 (5.6)
Fatigue	0	0	1 (16.7)	1 (5.6)
Arthralgia	0	1 (3.3)	0	1 (5.6)
Epistaxis	1 (10.0)	0	1 (16.7)	0
AEs of special interest				
Injection site reaction	0	1 (3.3)	0	0

Figure 2. Lp(a) Percent Change from Baseline After a Single Dose of Placebo or Olpasiran



Baseline values are the mean of screening and day 1 pre-dose values. If only 1 value was available, that value was used as the baseline value.
As of data snapshot date: 21Oct2020.

Results

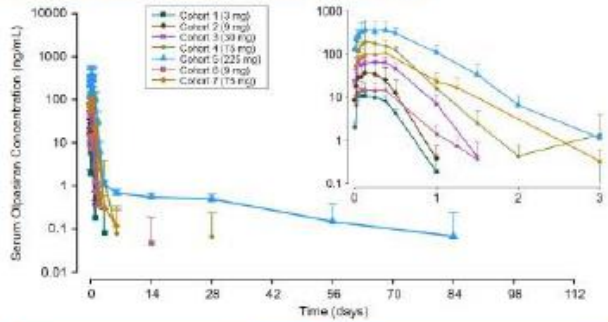
Table 2. Baseline Characteristics

Baseline Characteristic		Cohorts 1–5 Screening Lp(a) ≥70 to ≤199 nmol/L		Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L	
		Placebo (N=10)	Olpasiran (N=30)	Placebo (N=6)	Olpasiran (N=18)
Age (years), mean (SD)		46.3 (8.5)	43.9 (13.5)	57.8 (5.8)	52.7 (8.4)
Women, n (%)		3 (30.0)	9 (30.0)	4 (66.7)	6 (33.3)
Ethnicity, n (%)	Hispanic/Latino	5 (50.0)	19 (63.3)	2 (33.3)	5 (27.8)
	Not Hispanic/Latino	5 (50.0)	11 (36.7)	4 (66.7)	13 (72.2)
Race, n (%)	Black	3 (30.0)	9 (30.0)	0	1 (5.6)
	White	7 (70.0)	21 (70.0)	5 (83.3)	16 (88.9)
	Other	0	0	1 (16.7)	1 (5.6)
BMI, kg/m², mean (SD)		27.6 (3.5)	27.0 (3.6)	28.1 (2.1)	27.7 (3.3)
Lp(a) nmol/L, median (Q1, Q3)		124 (104, 137)	122 (97, 146)	272 (233, 307)	253 (224, 334)

Pharmacokinetic Results

- Olpasiran was rapidly absorbed with mean C_{max} occurring within 7.5 hours after dosing. Mean half-life ($t_{1/2}$) ranged from 3 to 8 hours with the vast majority eliminated from serum within 2 to 3 days
- Olpasiran AUC exposures in subjects with Lp(a) ≥200 nmol/L (Cohorts 6 and 7) were 18–33% lower than in subjects with Lp(a) ≥70 to ≤199 nmol/L (Cohorts 2 and 4)

Figure 3. Mean (SD) Serum Olpasiran Concentration-Time Profiles Following A Single SC Administration of 3, 9, 30, 75, or 225 mg



Conclusions

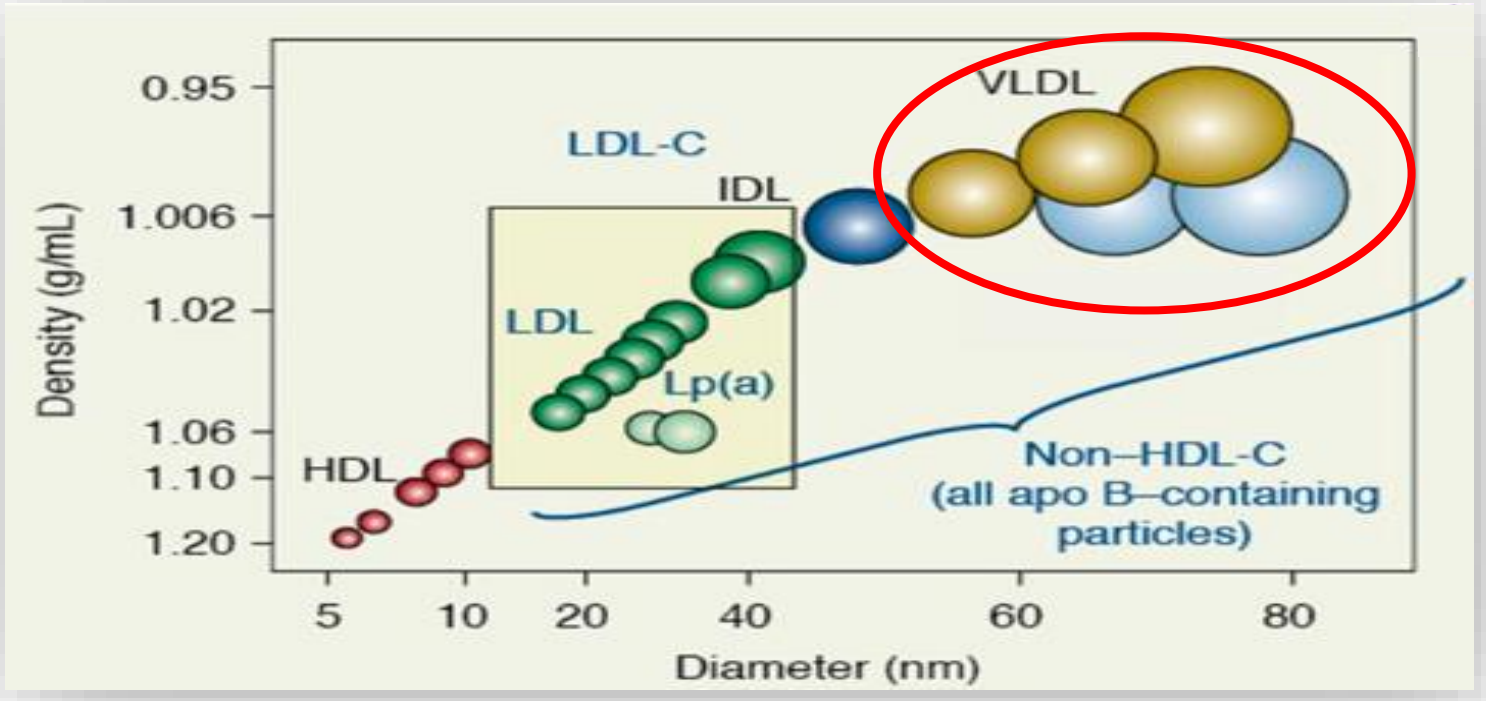
- No safety concerns were identified for olpasiran in this single dose study
  - No clinically relevant changes in liver tests, platelets or coagulation parameters, or renal function were observed
- Systemic exposures of olpasiran increased approximately dose-proportionally
- In adults with elevated Lp(a) (median Lp(a) = 122 nmol/L [cohorts 1 to 5] and 253 nmol/L [cohorts 6 and 7]), a single dose of olpasiran significantly reduced Lp(a) with observed approximate median percent reductions of >90% at doses of ≥9 mg in a dose-dependent manner
  - Lp(a) reductions persisted for 3 to 6 months at doses of ≥9 mg
  - Per the protocol, follow-up is ongoing until patients return to 80% of baseline Lp(a)
- These results validate the approach of using hepatocyte-targeted siRNA to lower Lp(a) in people with elevated Lp(a)
- Olpasiran recently received a Fast Track Designation from the US Food and Drug Administration. A Phase 2 study to evaluate efficacy, safety, and tolerability of olpasiran in subjects with elevated Lp(a) is currently underway

References

1. Nordestgaard BG, et al. *Eur Heart J*. 2010;31:2844-2853.
2. Wilson DP, et al. *J Clin Lipidol*. 2019;13(2):374-392.
3. Madsen CM, et al. *Eur Heart J*. 2020;41(1):111-188.

Characteristics of lipoproteins

Remnants cholesterol



Lowering Remnant cholesterol with Apo-CIII-antisense

‘Remnant’ cholesterol is next on the list

Apo-CIII antisense reduces TG and remnant cholesterol

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.

Table 2. Absolute Levels of ANGPTL3, Lipids, and Lipoproteins at Day 43 after Initiation of ANGPTL3-L_{Rx} Treatment in the Multiple-Dose Groups.*

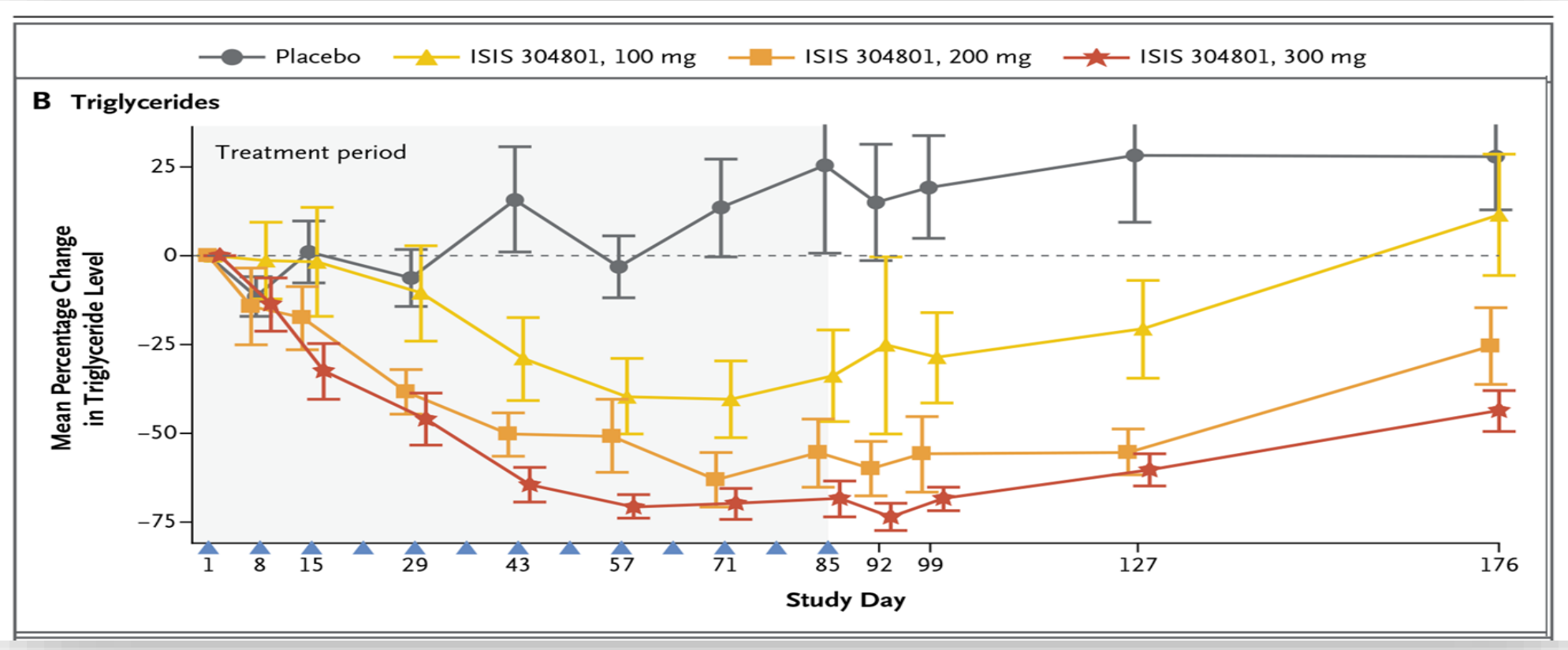
Measure	Placebo (N=8)	ANGPTL3-L_{Rx}			
		10 mg (N=6)	20 mg (N=5)	40 mg (N=6)	60 mg (N=6)
ANGPTL3 — ng/ml	132.5±38.9	45.3±22.9†	24.5±7.5†	21.1±5.0†	16.6±8.1†
Triglycerides — mg/dl	183±76	135±55	73±20†	93±24‡	82±27†
LDL cholesterol — mg/dl	151±18	126±29	124±24	115±31‡	85±26†
VLDL cholesterol — mg/dl	37±15	27±11	15±4†	19±5‡	16±6†
Apolipoprotein B — mg/dl	122±19	102±22	99±13‡	90±19‡	78±22†
Non-HDL cholesterol — mg/dl	188±25	153±28‡	139±26‡	133±32‡	101±31†
Total cholesterol — mg/dl	230±20	197±27‡	171±30†	168±33†	134±29†
HDL cholesterol — mg/dl	42±12	44±16	32±5	35±4	33±10
Apolipoprotein AI — mg/dl	146±15	143±36	115±15†	112±13†	105±23†
Apolipoprotein C-III — mg/dl	12.8±3.2	9.1±3.8	4.2±2.3†	5.7±3.1†	3.8±1.0†
Lipoprotein(a) — nmol/liter	32±21	71±69	13±12	18±24	5±8†

NEJM 2017;377:222

Lowering Remnant cholesterol with Apo-CIII-antisense

‘Remnant’ cholesterol is next on the list

Apo-CIII antisense reduces TG and remnant cholesterol



NEJM 2017;377:222

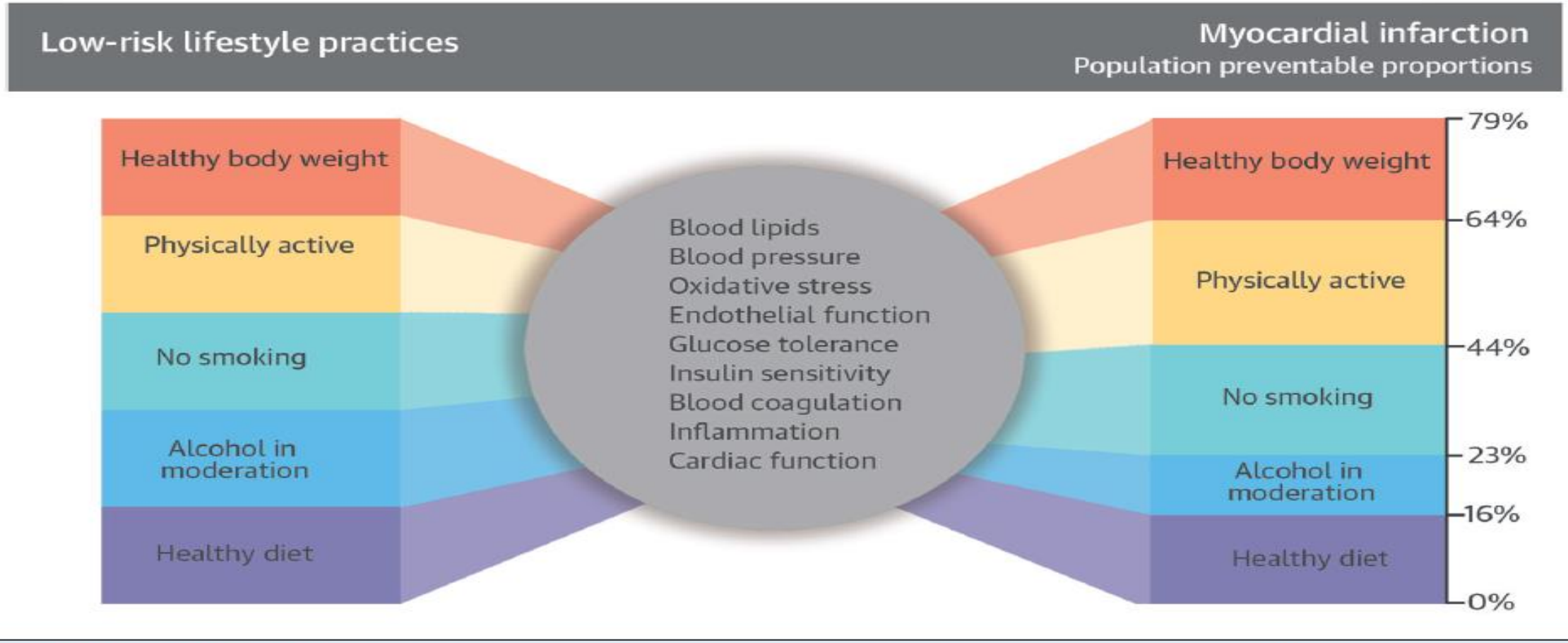
Consultation “Lipides” aux HUG

- Consultation conjointe des **Services de Cardiologie** et **d’Endocrinologie**
  Prof. François Jornayvaz, Prof. Georg Ehret, Prof. François Mach
- Infirmière coordinatrice: Mme Elise Guillermet
  Tél: 079-553 55 08 Fax: 022-372 50 18 elise.guillermet@hcuge.ch



Hôpitaux Universitaires Genève

CV Risk factors & lifestyle



CENTRAL ILLUSTRATION **5 Combined Low-Risk Behaviors and the Population Preventable Proportions of MI**

The combination of the 5 low-risk dietary and lifestyle factors, the proposed intermediate biological factors, and the population preventable proportions of myocardial infarction.

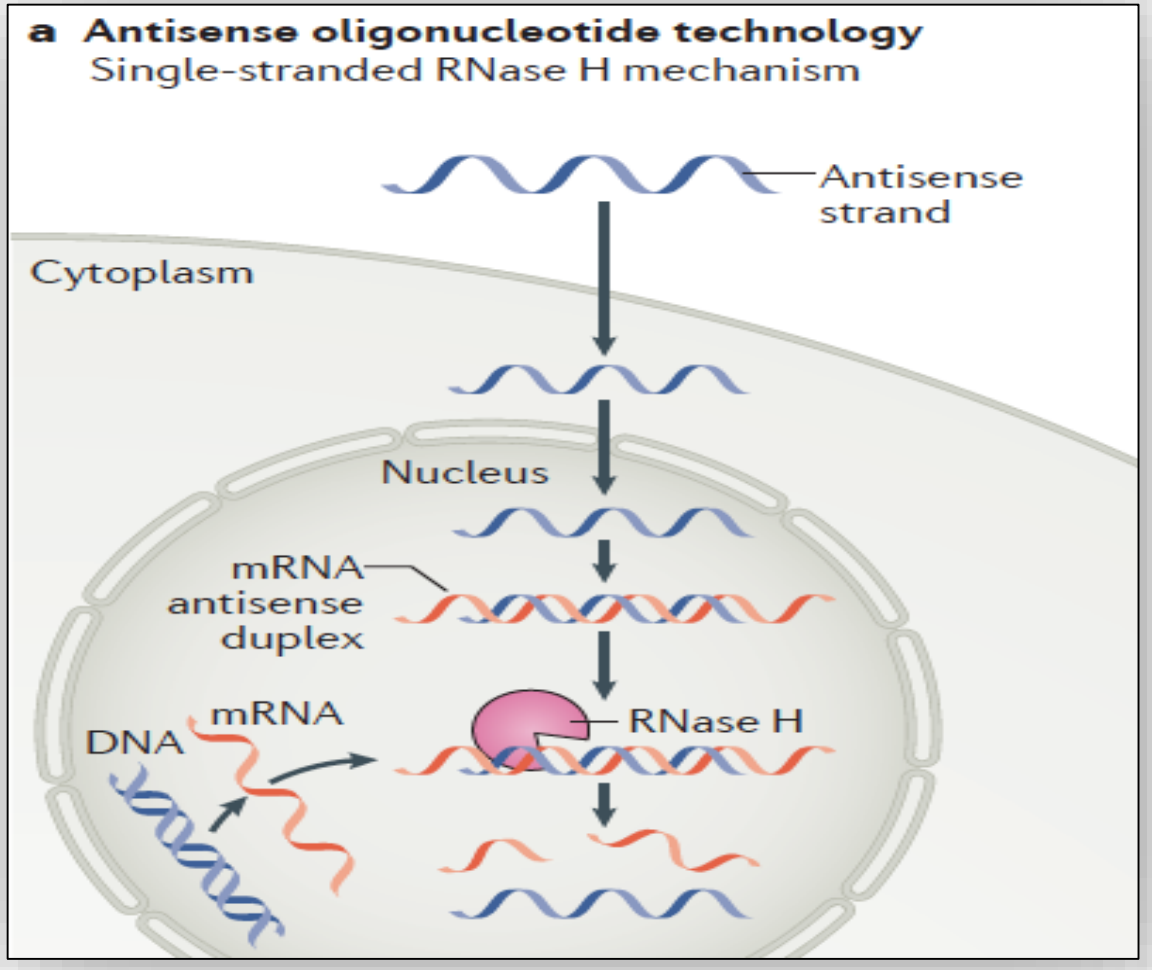
JACC 2014;64:93:12997

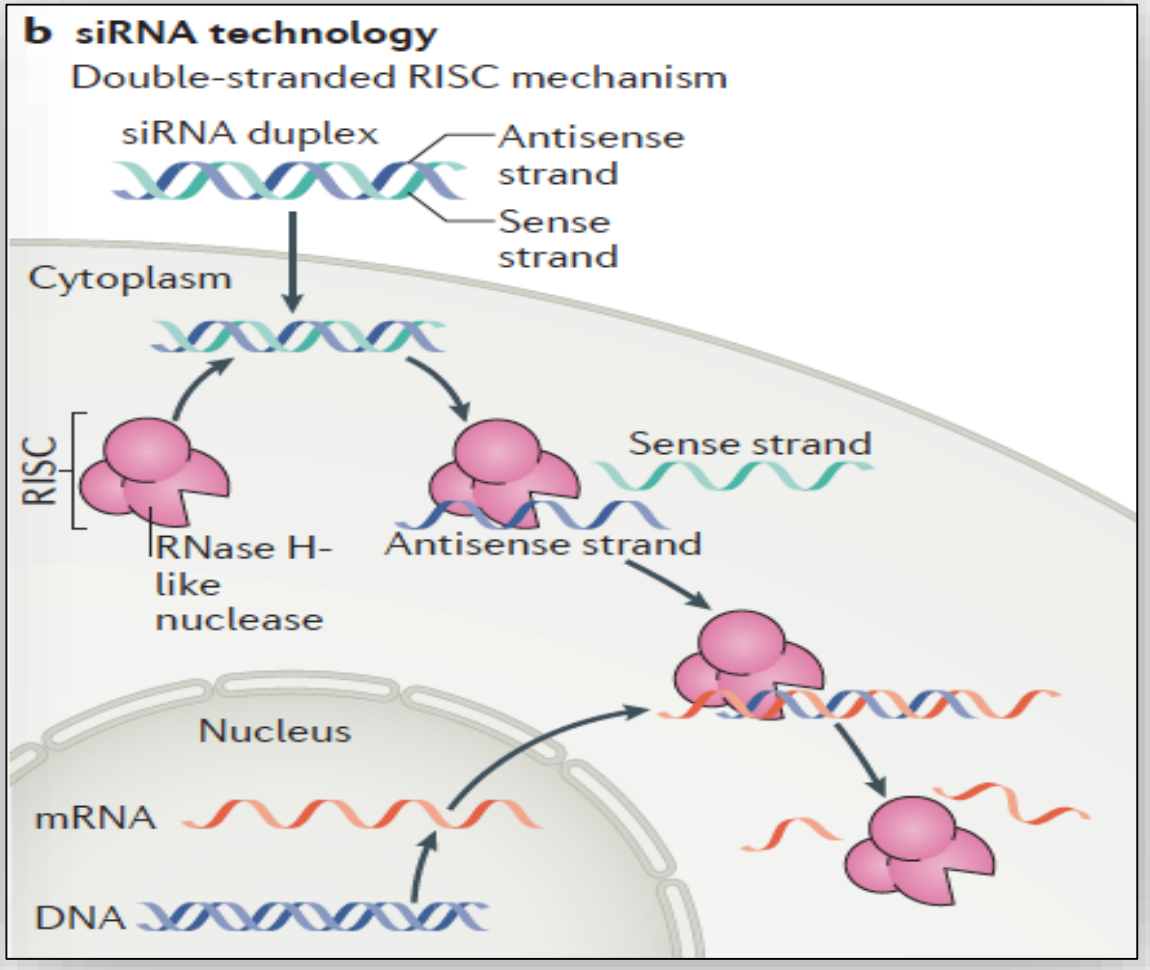
Service de cardiologie / HUG
Colloque multidisciplinaire de formation continue, cardiologie et chirurgie cardio-vasculaire
Genève, le 27 mai 2021

Merci pour votre attention

Genetic-therapy to reduce blood-lipid-levels

Antisense oligonucleotide-based versus siRNA-based approaches





Nature Rev Cardiol May 2018;15:261

Remnant cholesterol causally related to CVD-risk: *Mendelian Randomization*

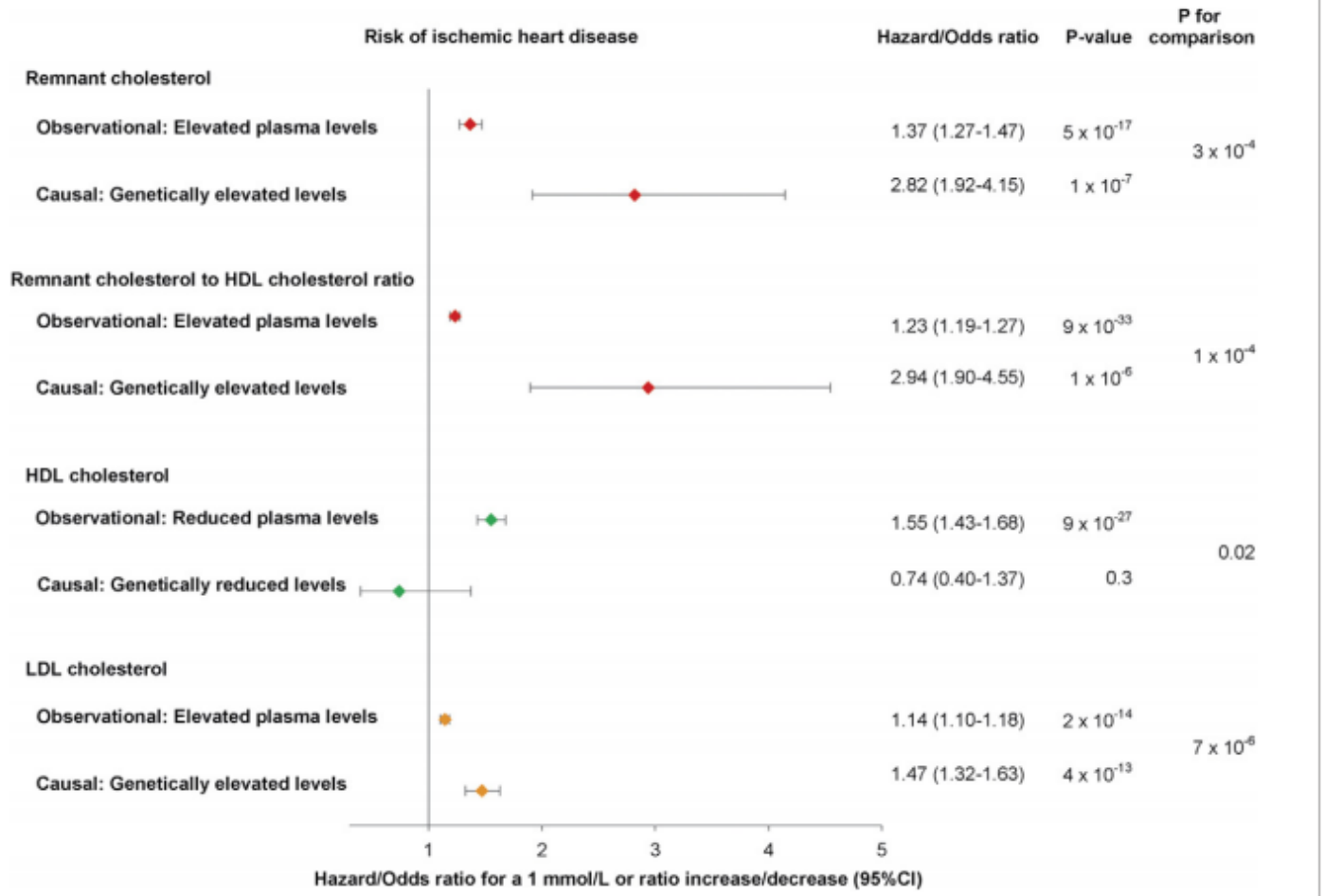


Figure 6 Causal and Observational Risk Estimates for Ischemic Heart Disease

Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease

Anette Varbo, MD,*†‡ Marianne Benn, MD, PHD, DMSC,*†‡
Anne Tybjærg-Hansen, MD, DMSC,†‡§‖ Anders B. Jørgensen, MD,†‡§
Ruth Frikke-Schmidt, MD, PHD, DMSC,†‡§ Børge G. Nordestgaard, MD, DMSC*†‡§