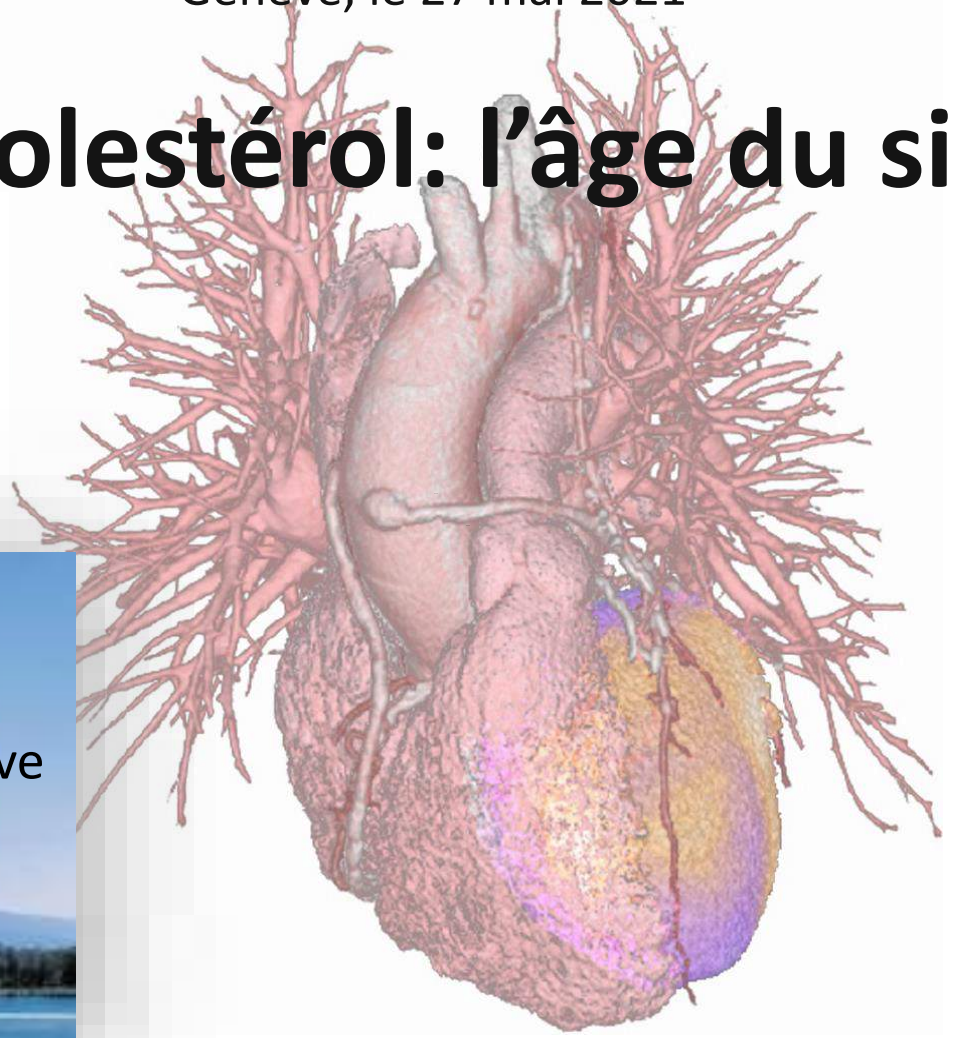
Service de cardiologie / HUG
Colloque multidisciplinaire de formation continue, cardiologie et chirurgie cardio-vasculaire
Genève, le 27 mai 2021

# LDL-cholestérol: l'âge du silence



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Service de Cardiologie
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Service de Cardiologie

HUG Hôpitaux Universitaires Genève

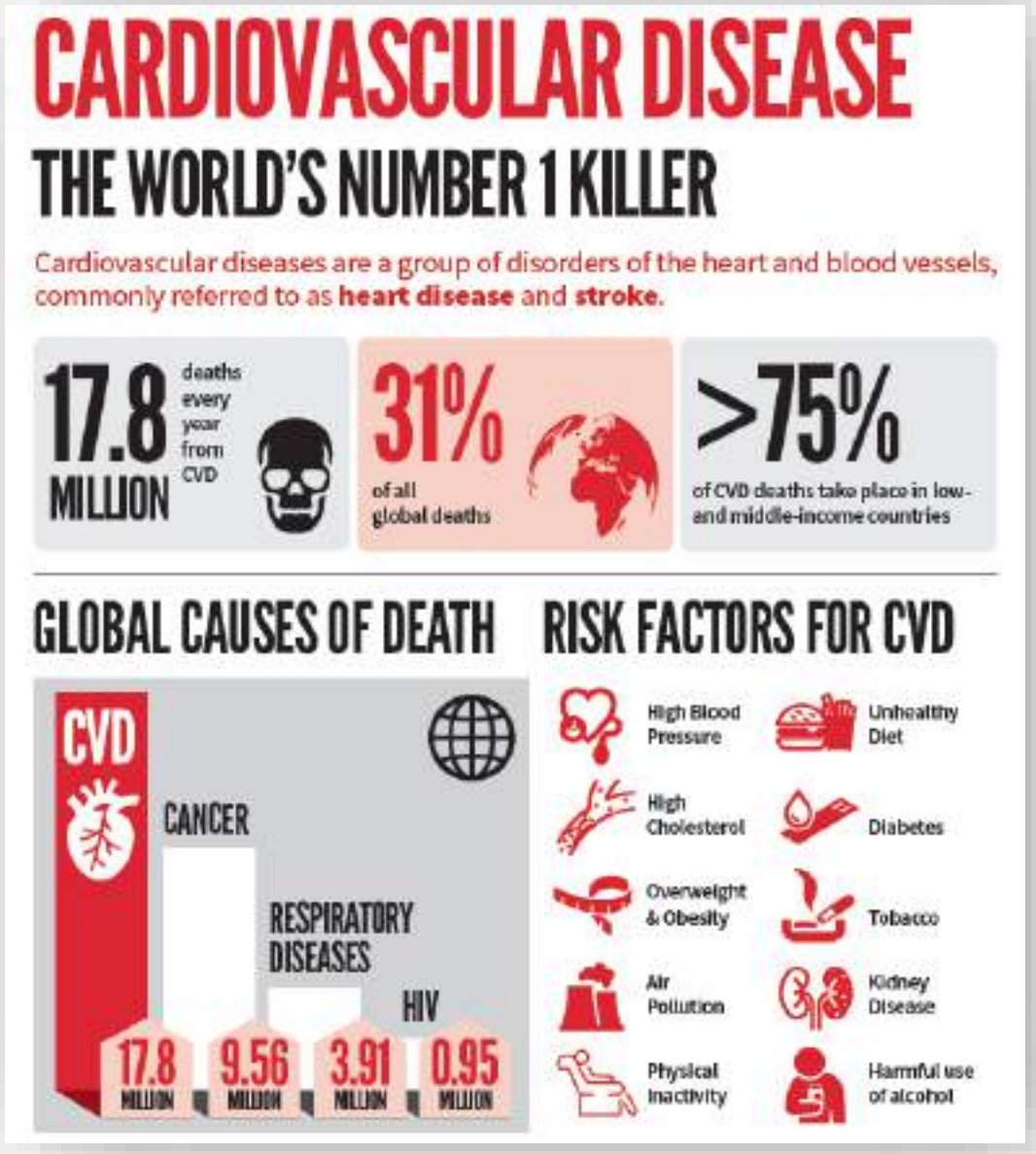
UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

## 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.

# Maladies cardiovasculaires



# Athérosclérose

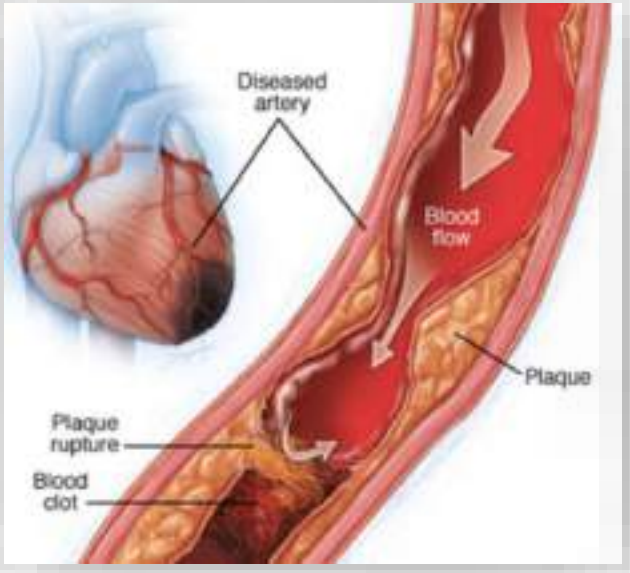
## Coronary Artery Disease

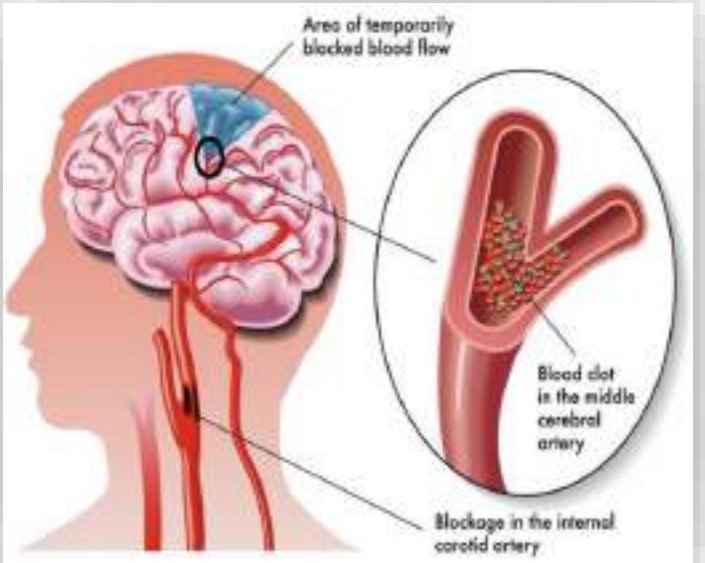
- Leading cause of mortality
- Happened globally
- Increase new cases
- Leading cause of loss of productivity

**TRUE PANDEMIC**

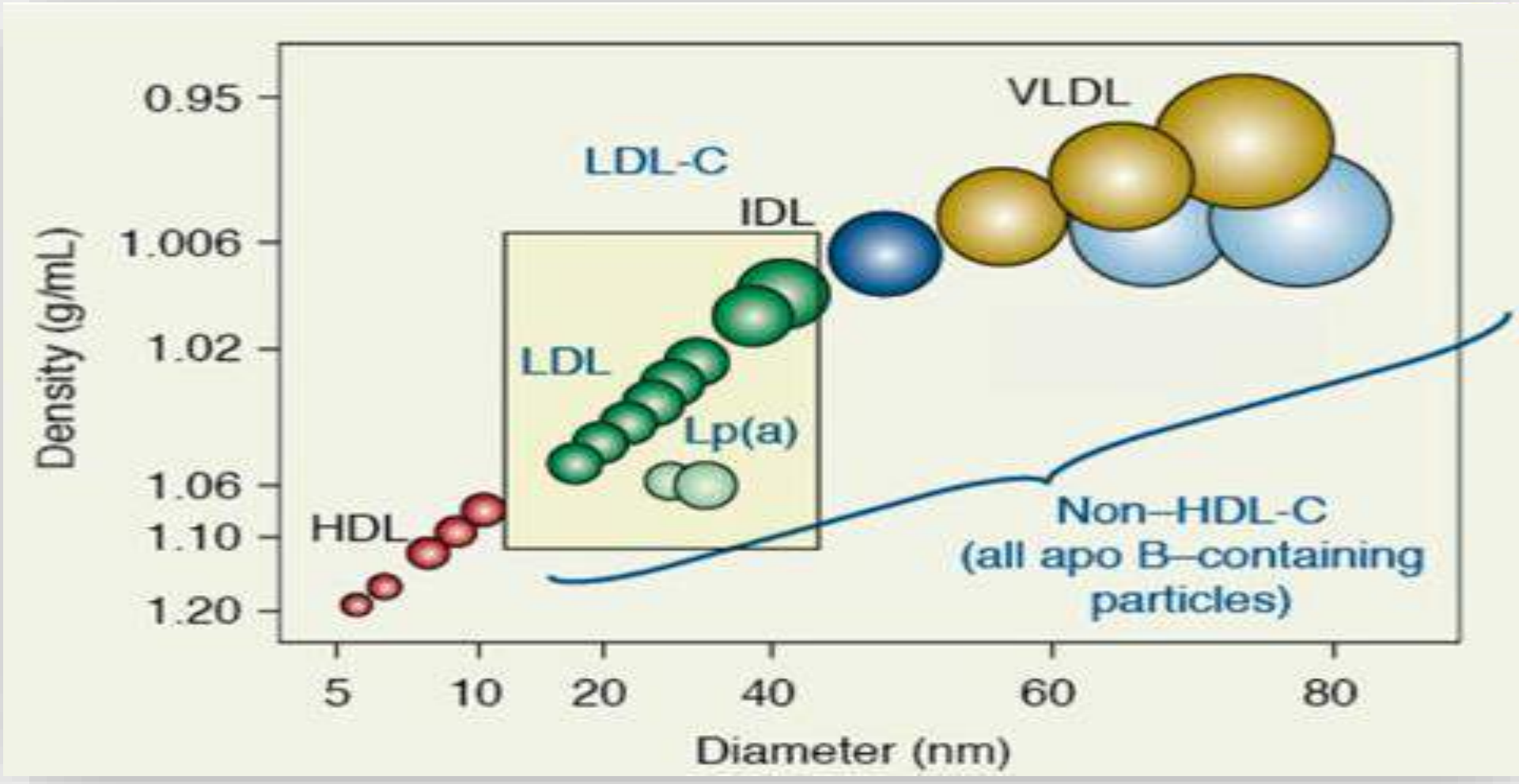
WHO (2009):

"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



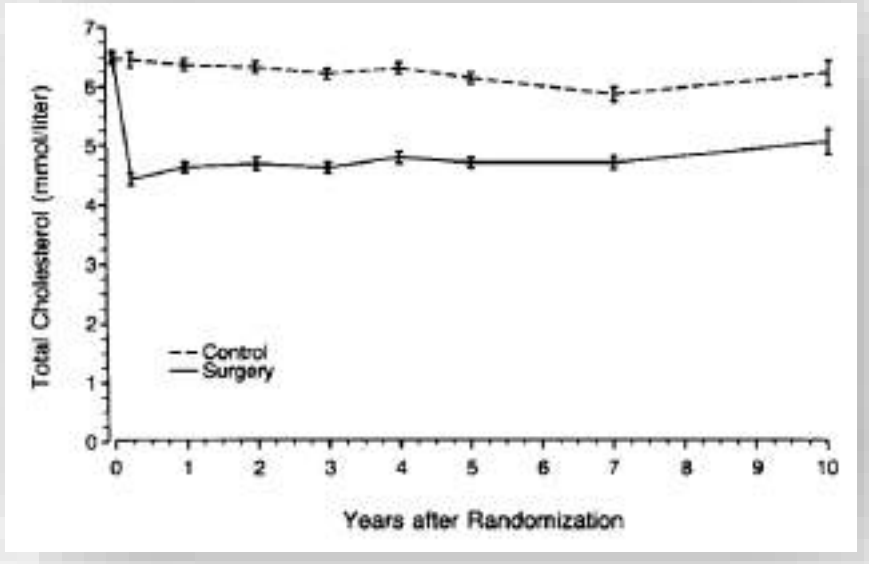
# Lowering cholesterol lowers CV events: first evidence



**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*



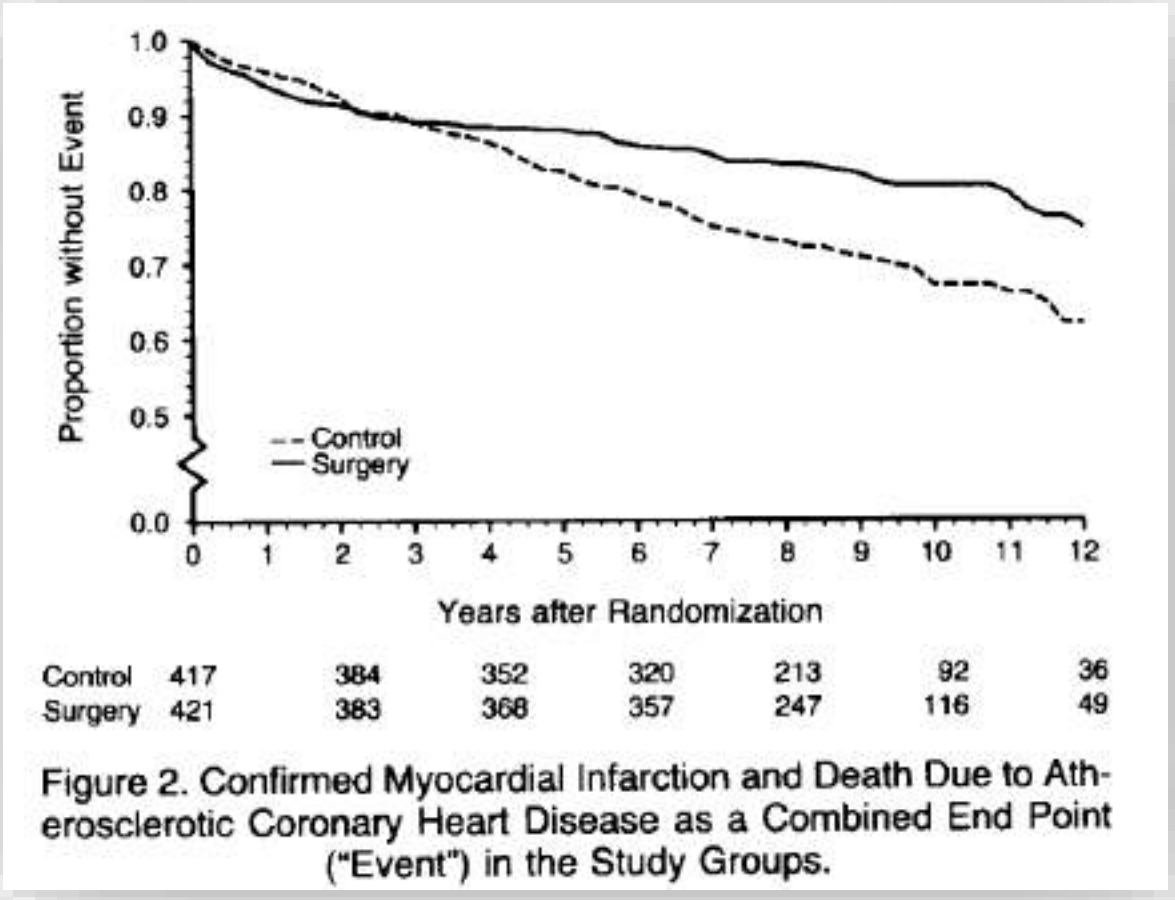
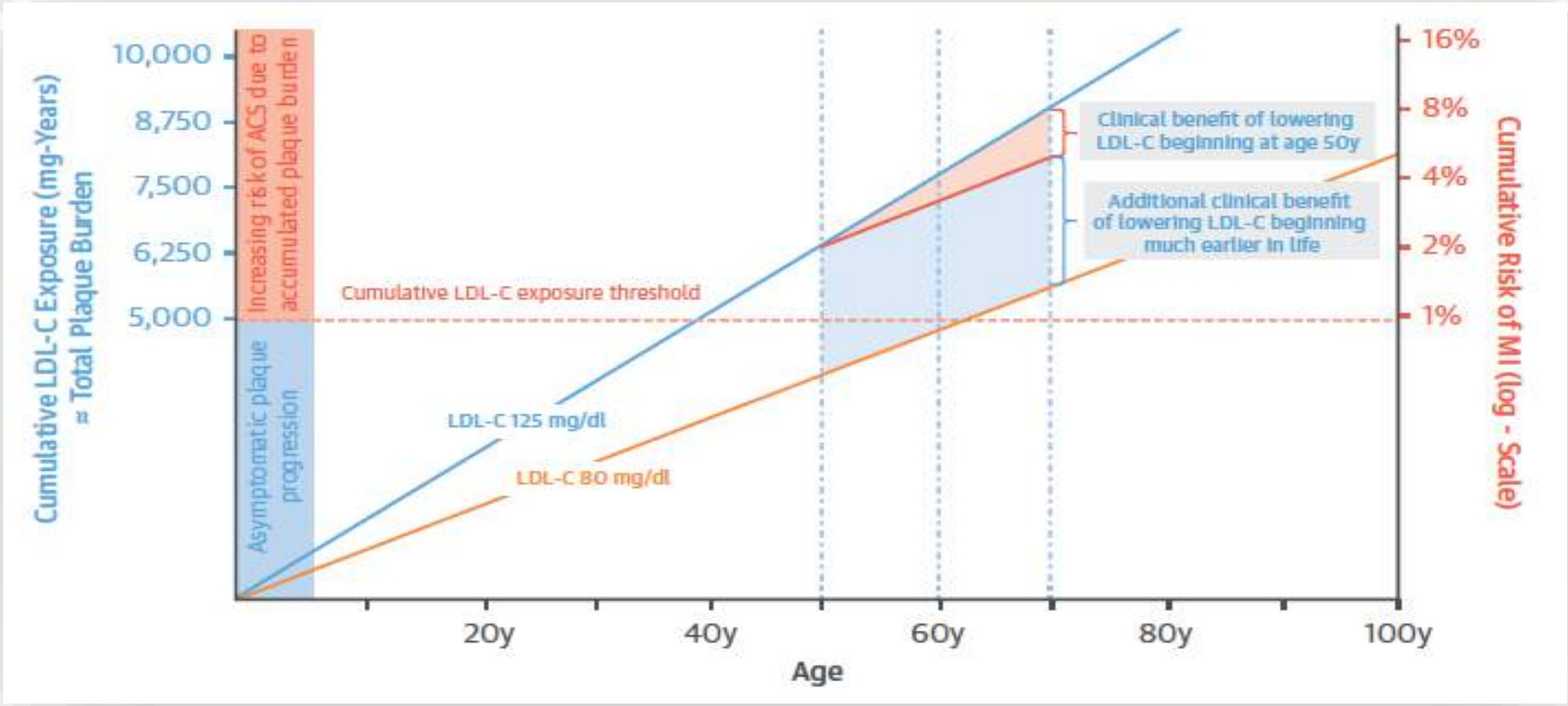




Figure 2. Confirmed Myocardial Infarction and Death Due to Atherosclerotic Coronary Heart Disease as a Combined End Point ("Event") in the Study Groups.

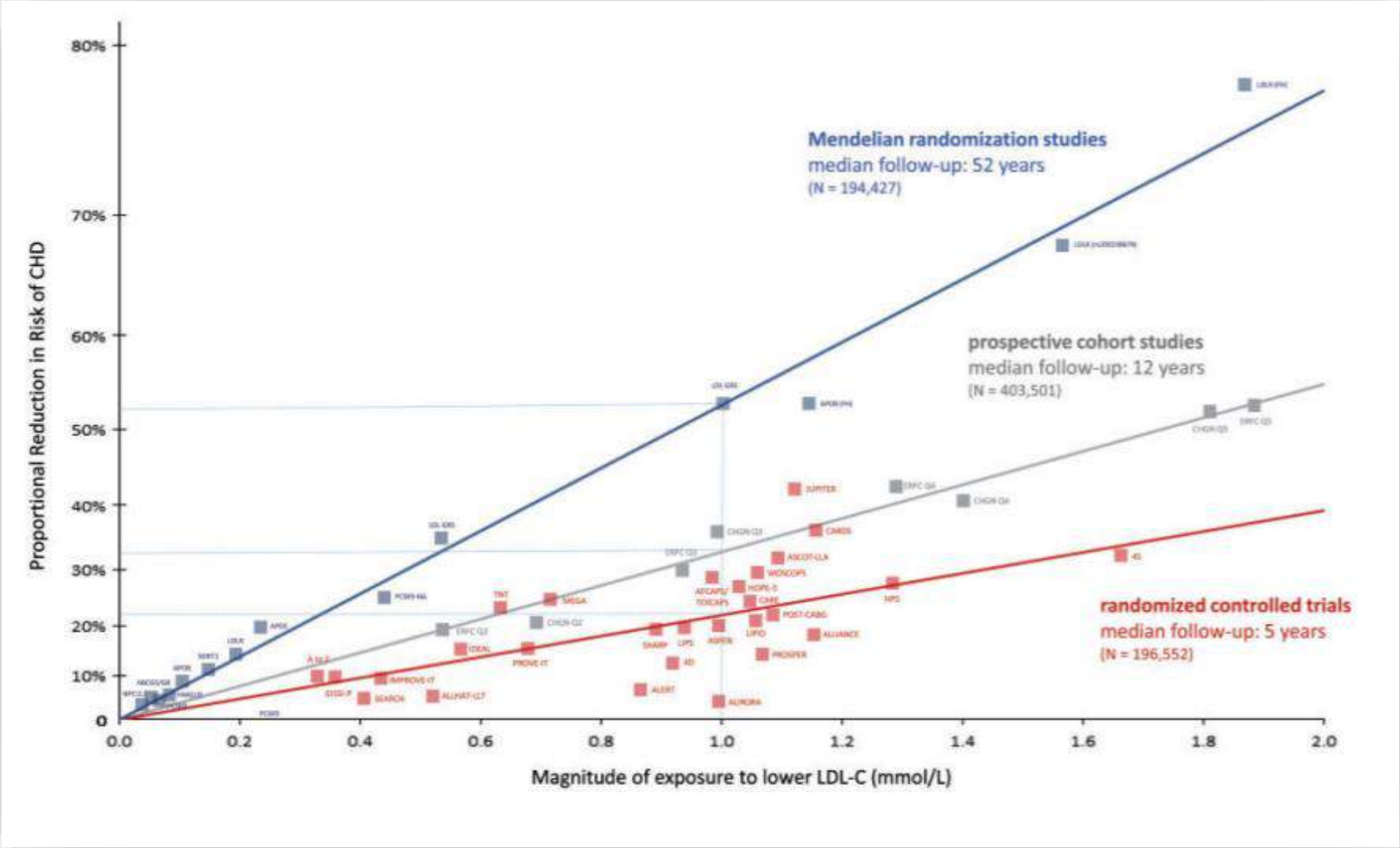
*N Engl J Med* 1990;323:946

# Time-Exposure to LDL-C



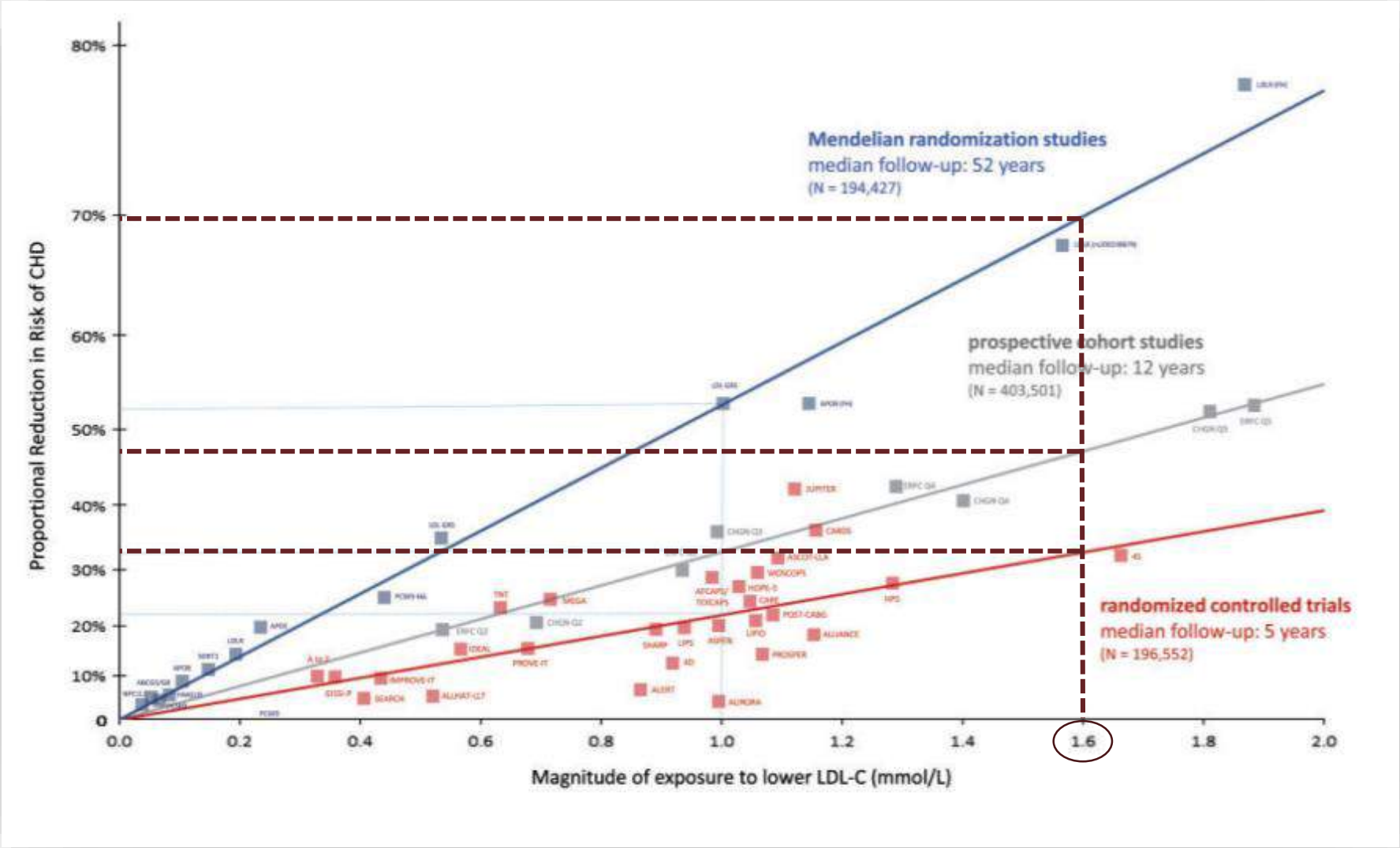

*JACC* 2018;72:2890

# 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

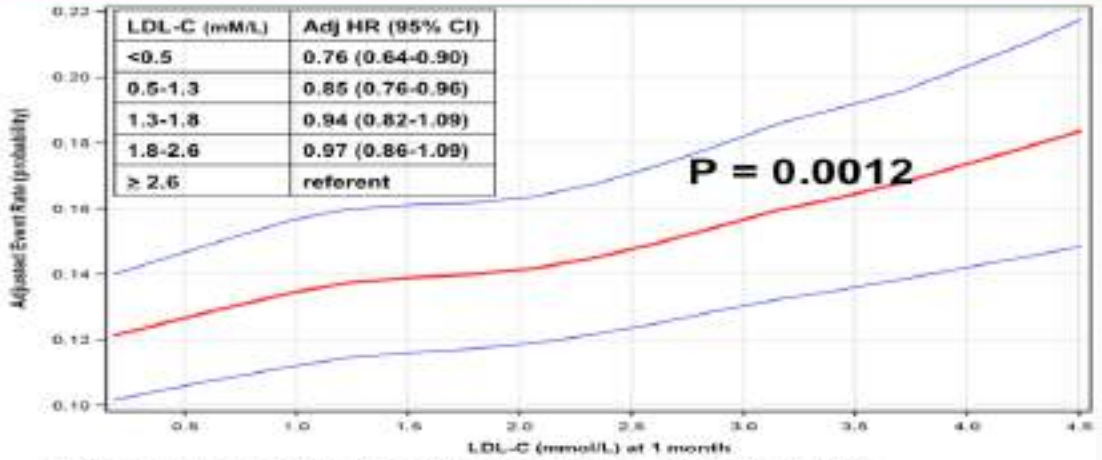
# PCSK9 mAb: Efficacy and safety

## 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 |



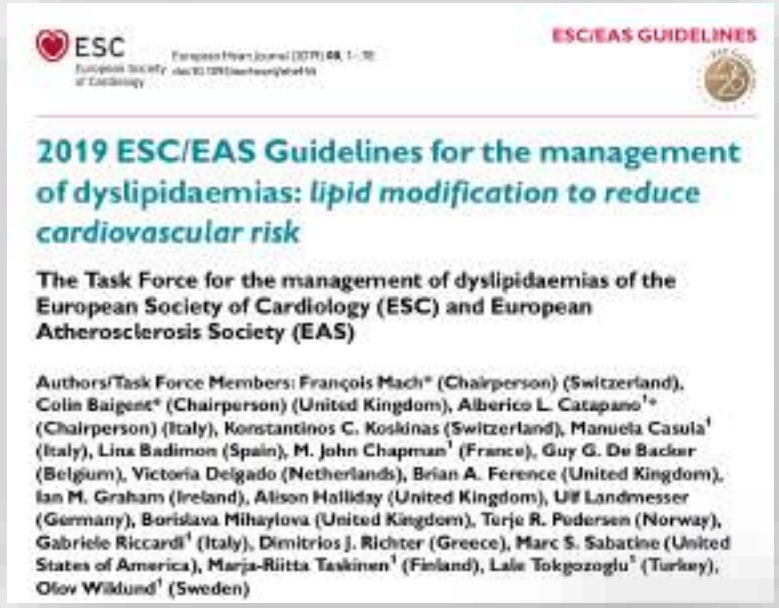

*CV death, MI, stroke, hospitalization for UA, coronary revasc

## 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



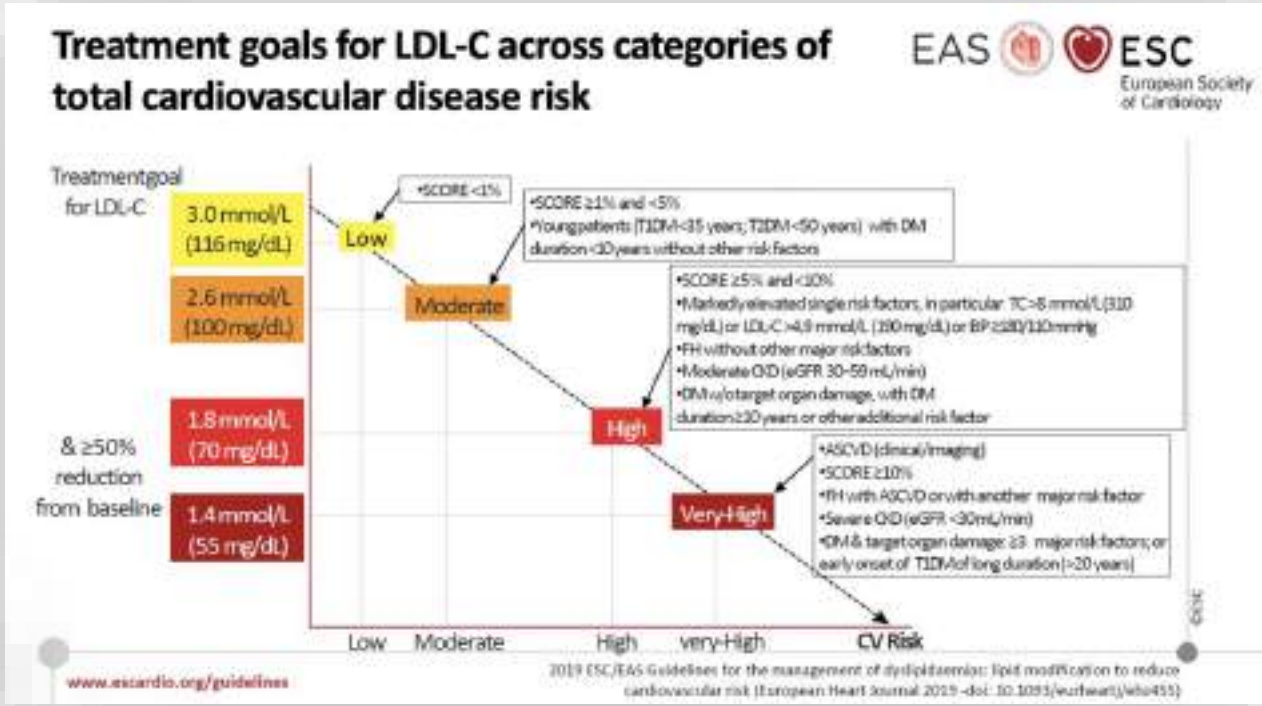
ESC

ESC/EAS GUIDELINES

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

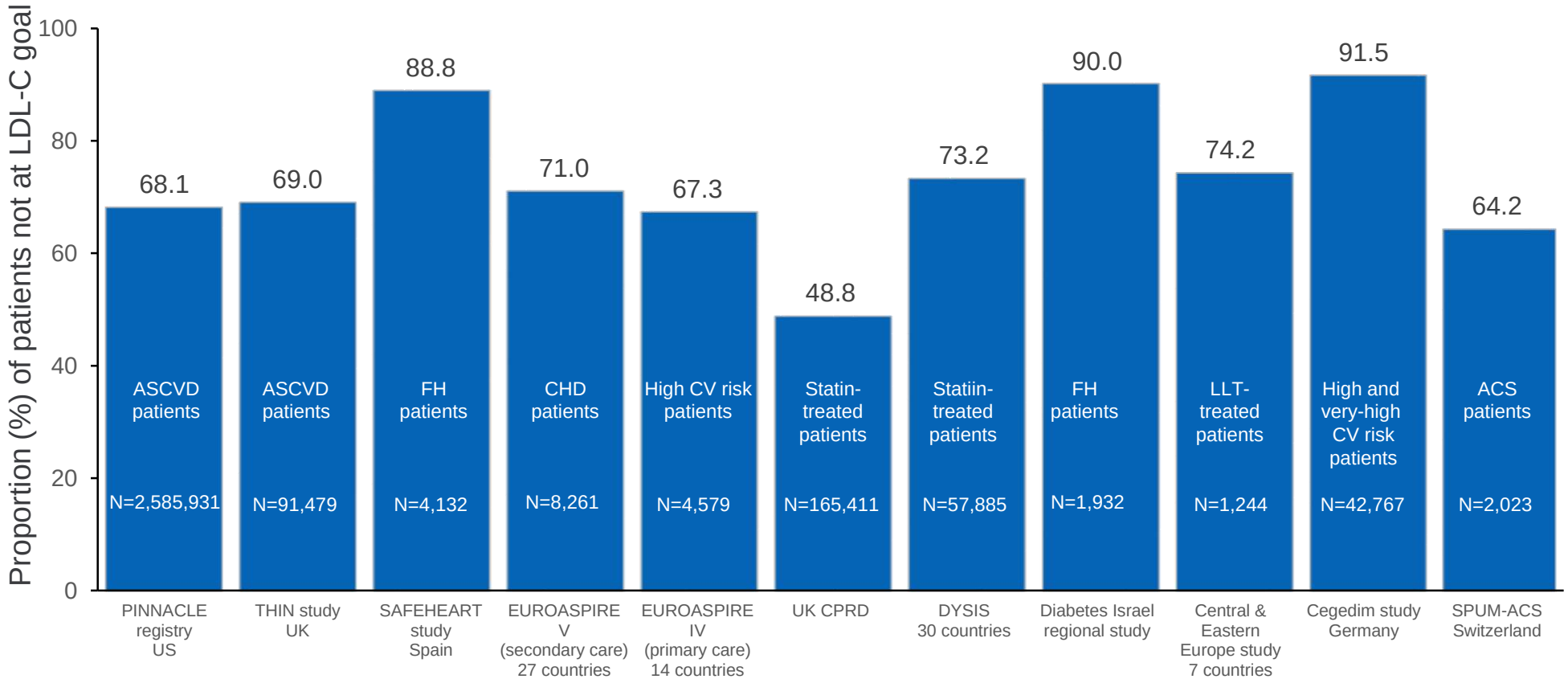
**The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)**

**Authors/Task Force Members: François Mach* (Chairperson) (Switzerland), Colin Baigent* (Chairperson) (United Kingdom), Alberico L. Catapano†* (Chairperson) (Italy), Konstantinos C. Koskinas (Switzerland), Manuela Casula† (Italy), Lina Badimon (Spain), M. John Chapman† (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† (Italy), Dimitrios J. Richter (Greece), Marc S. Sabatine (United States of America), Marja-Riitta Taskinen† (Finland), Lale Tokgozoglu† (Turkey), Olov Wiklund† (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**

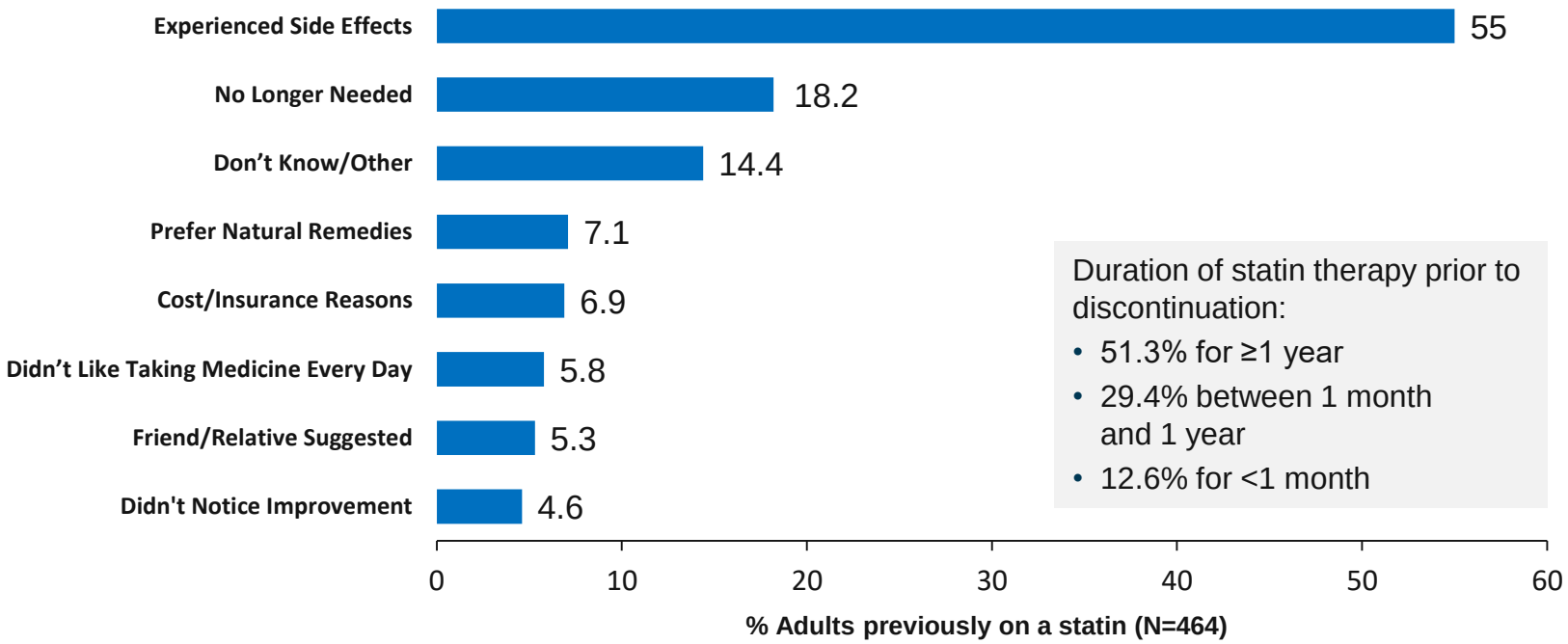
- Lack of HCP familiarity with guidelines
- High cost of medications such as PCSK9 mAb inhibitors
- Patient reluctance to be treated with high-intensity LLT
- Concern about statin-related AEs

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

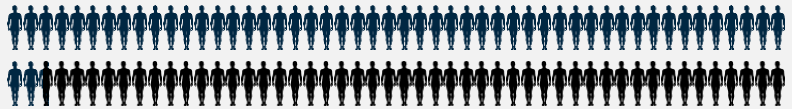
# Therapy interruptions are observed with monoclonal antibodies directed against PCSK9

**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



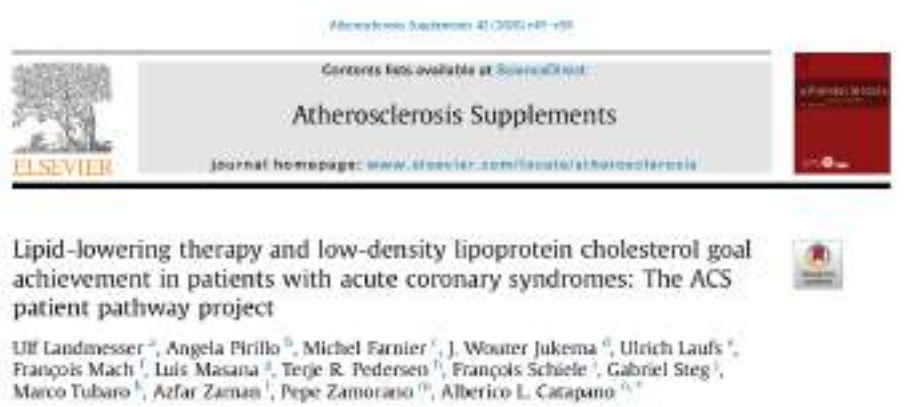
## 44% of patients

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

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

Ulf Landmesser, Angela Pirillo, Michel Farnier, J. Wouter Jukema, Ulrich Laufs, François Mach, Luis Masana, Terje R. Pedersen, François Schiele, Gabriel Steg, Marco Tubaro, Azfar Zaman, Pepe Zamorano, Alberico L. Catapano

*Atherosclerosis* 2020;40:e49-e58

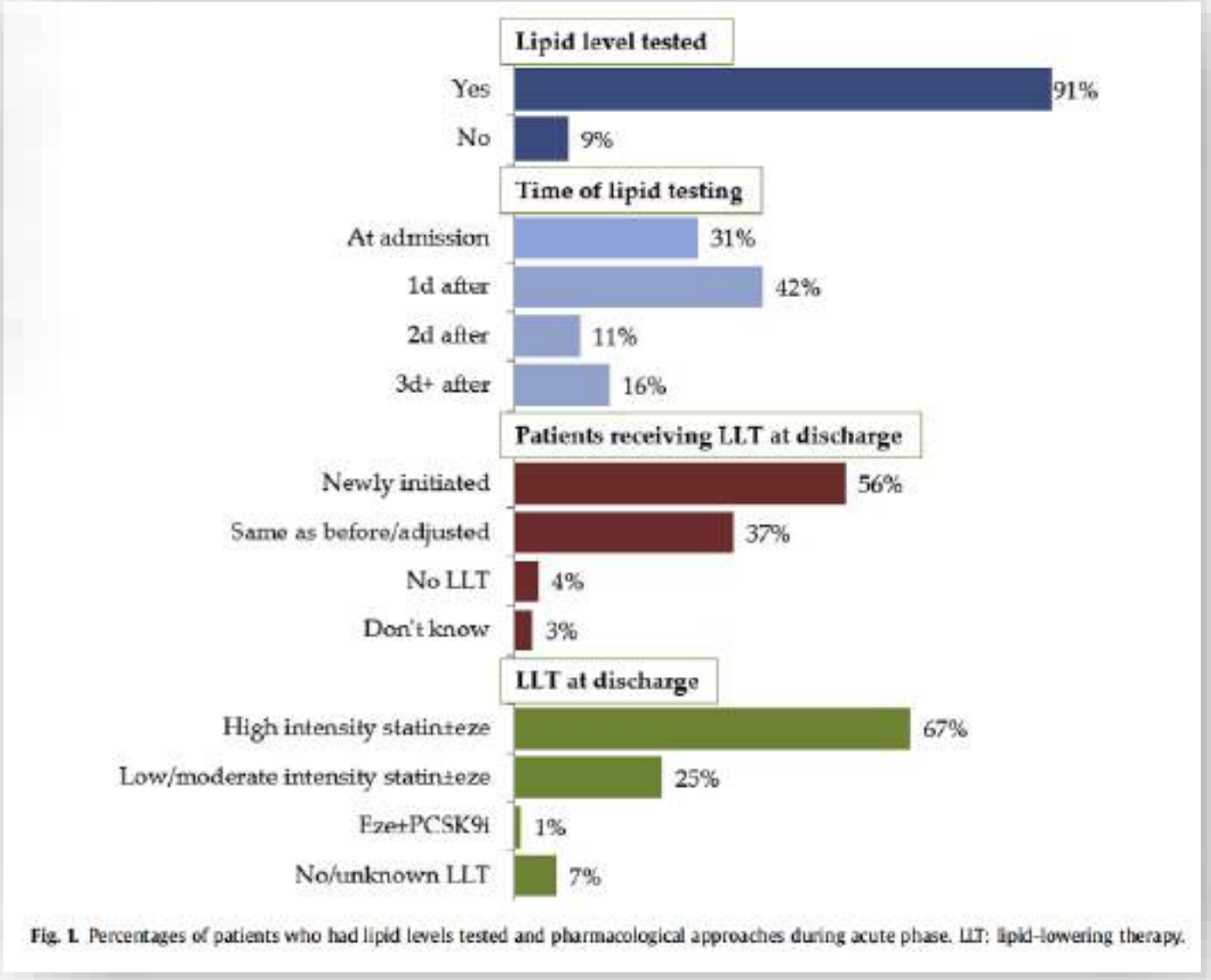



Fig. 1. Percentages of patients who had lipid levels tested and pharmacological approaches during acute phase. LLT: lipid-lowering therapy.

# Research on ACS management

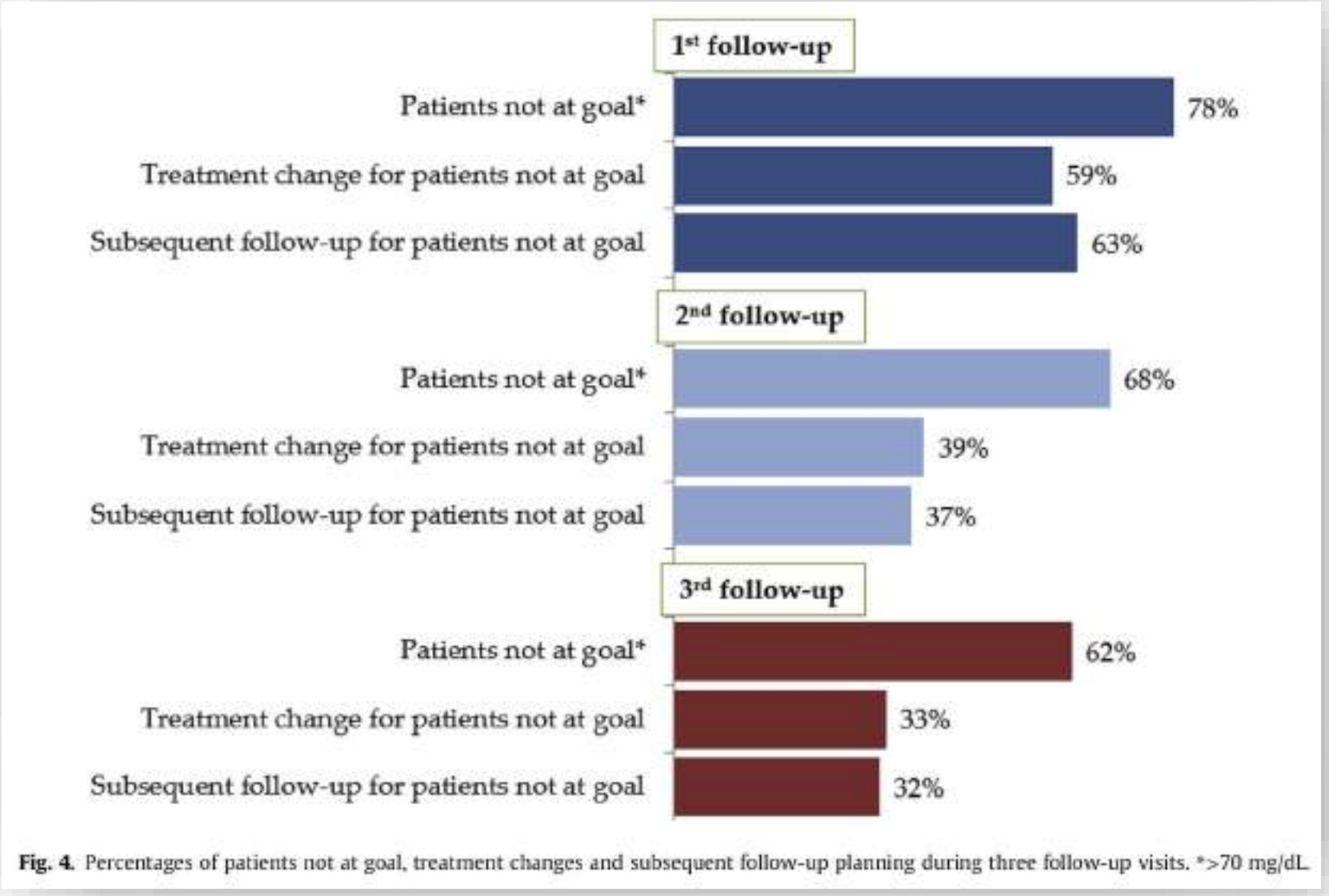



**Fig. 4.** Percentages of patients not at goal, treatment changes and subsequent follow-up planning during three follow-up visits. *>70 mg/dL.

*Atherosclerosis* 2020;40:e49-e58

# Research on ACS management

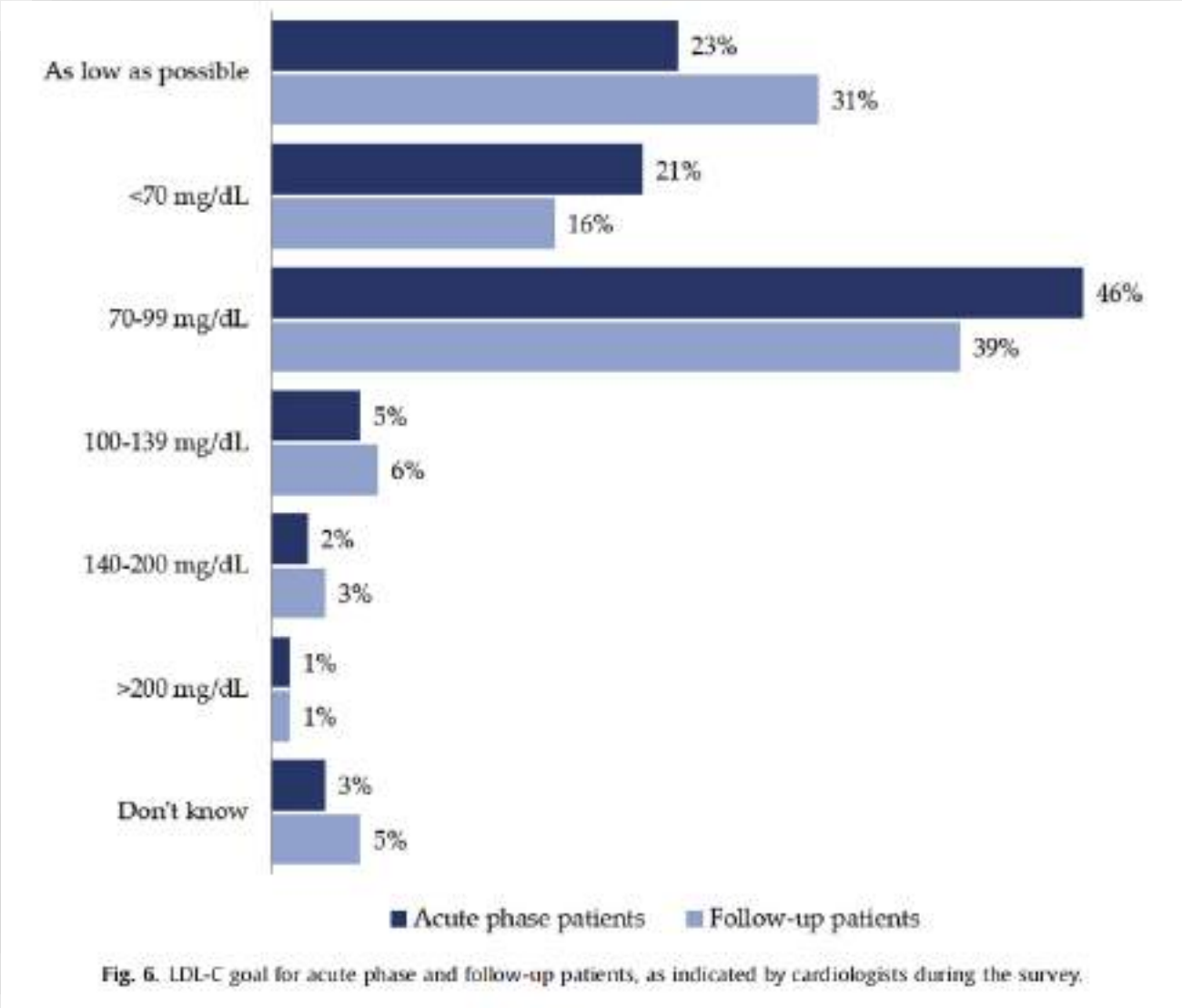
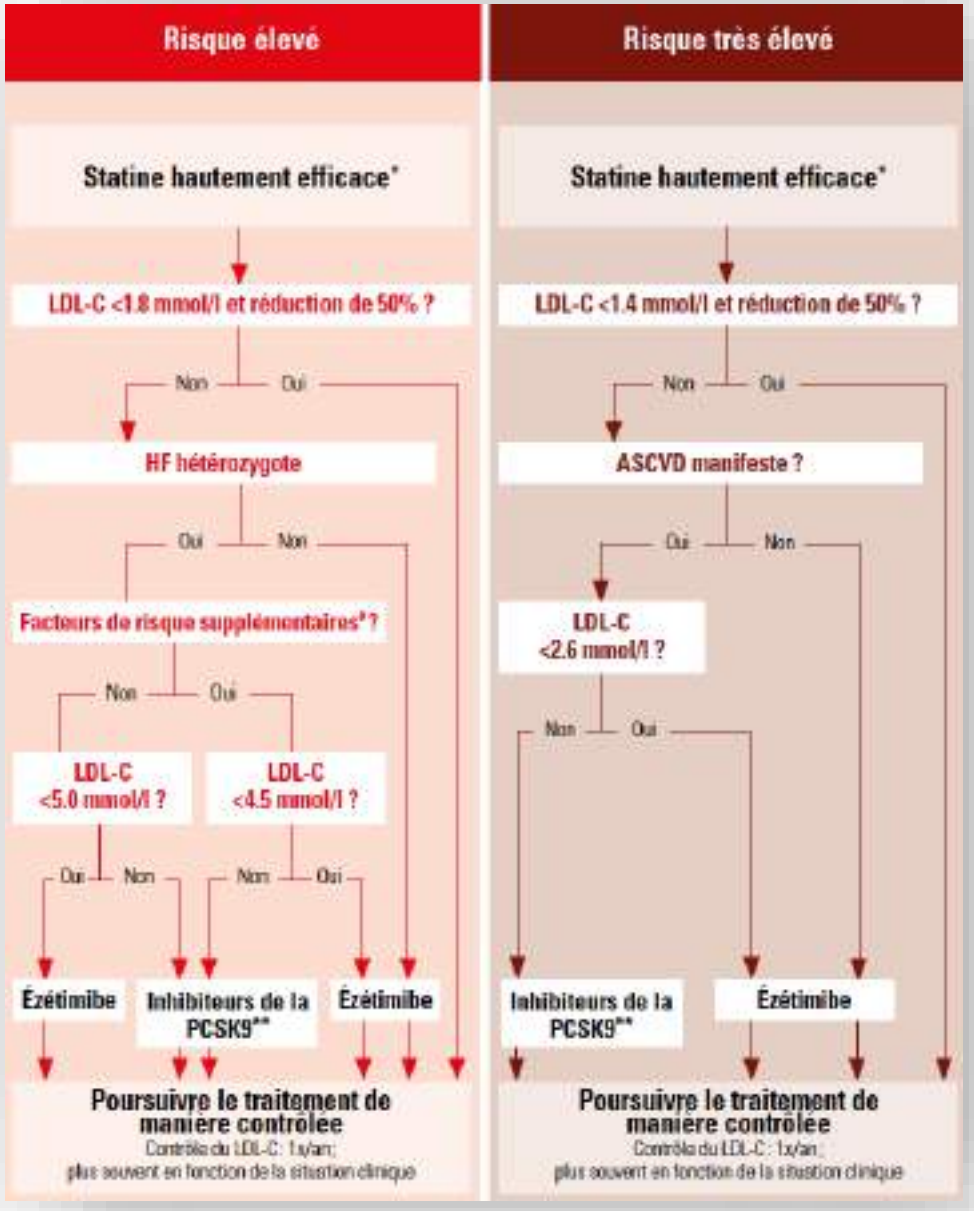


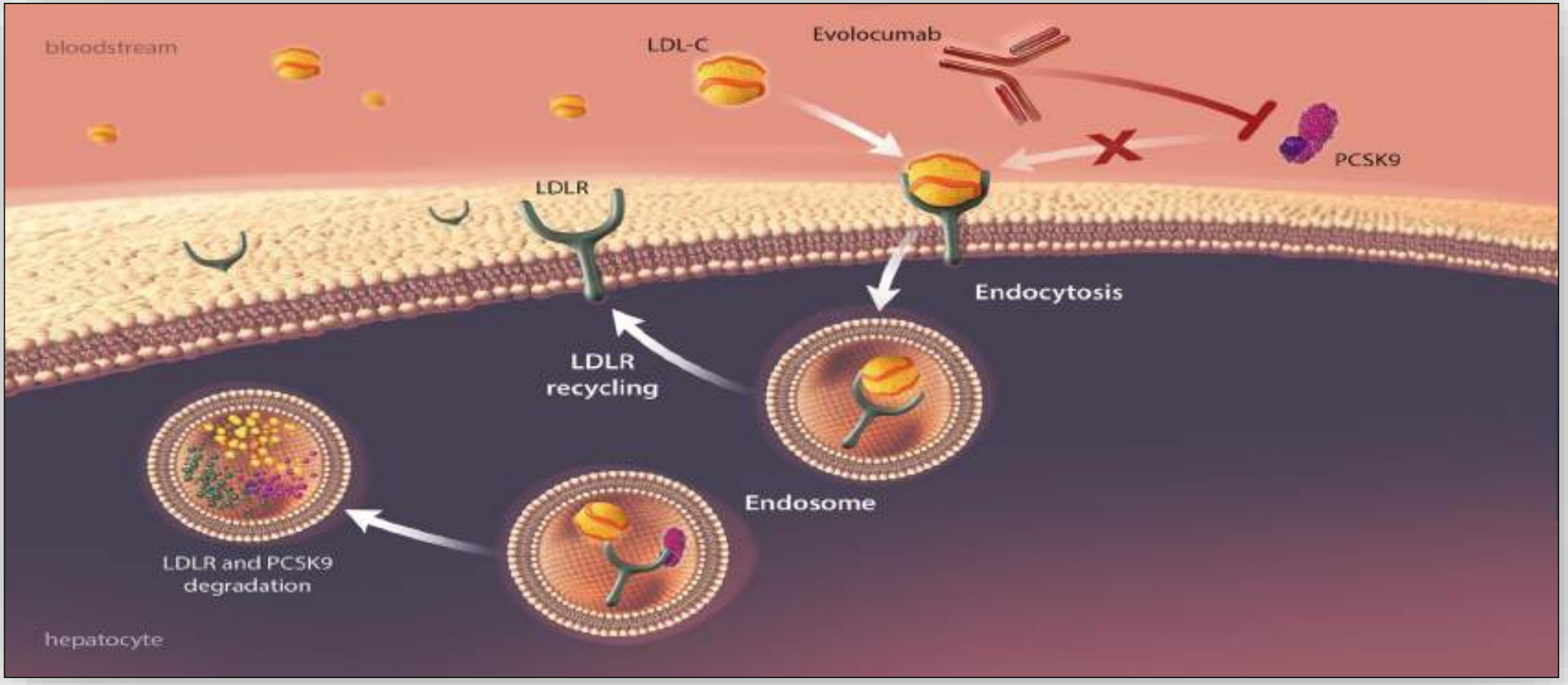

Fig. 6. LDL-C goal for acute phase and follow-up patients, as indicated by cardiologists during the survey.

*Atherosclerosis* 2020;40:e49-e58

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

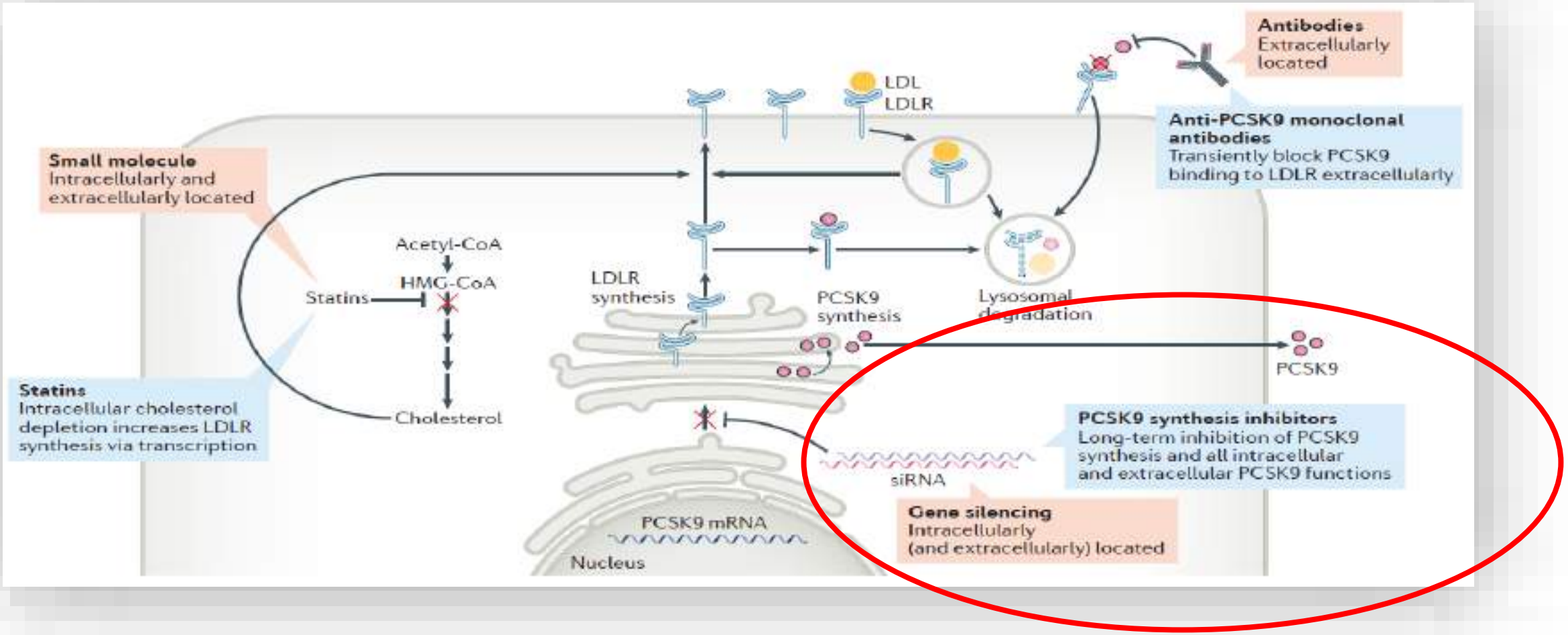


# Fully human monoclonal antibody against PCSK9 inhibits PCSK9/LDL-R interaction




*PNAS* 2009;106:9820

# Approaches to reduce LDL-C levels



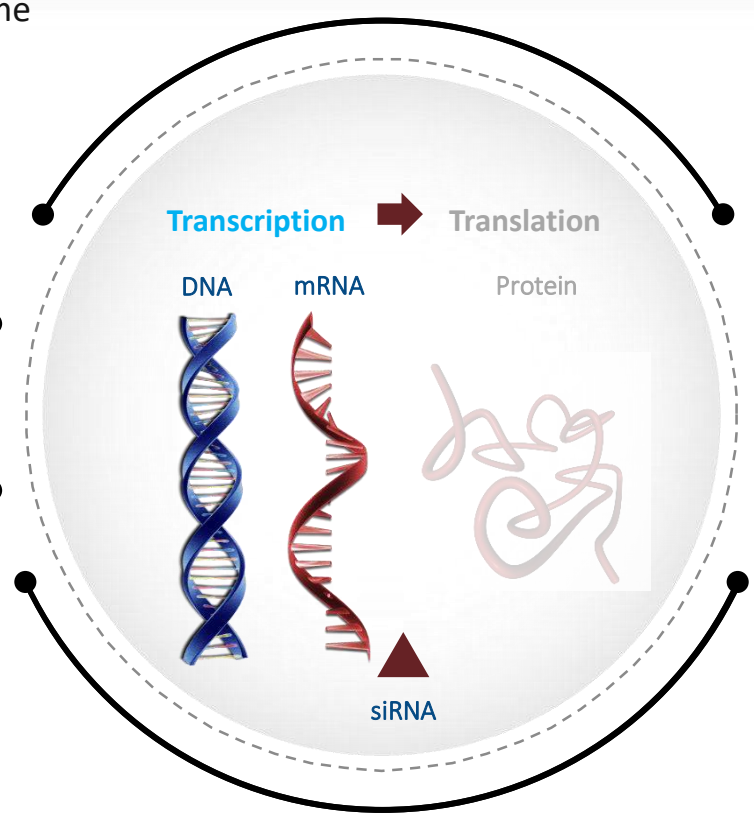

*Nature Rev Cardiol* 2018;15:261

# 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]



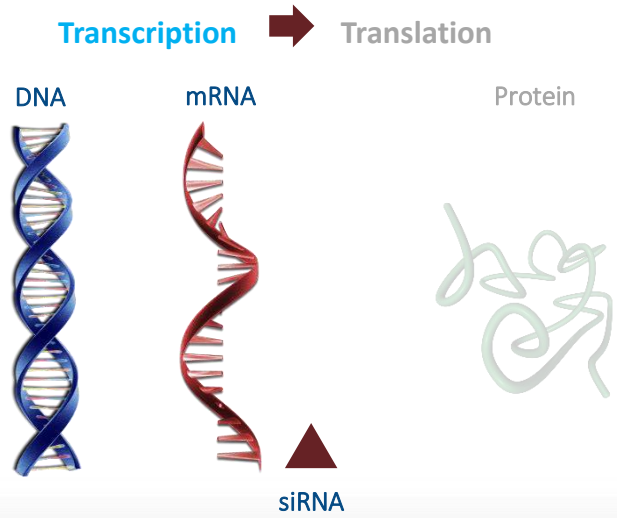

ncRNAs are involved in **gene regulation**, RNA maturation and protein synthesis[1]

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]

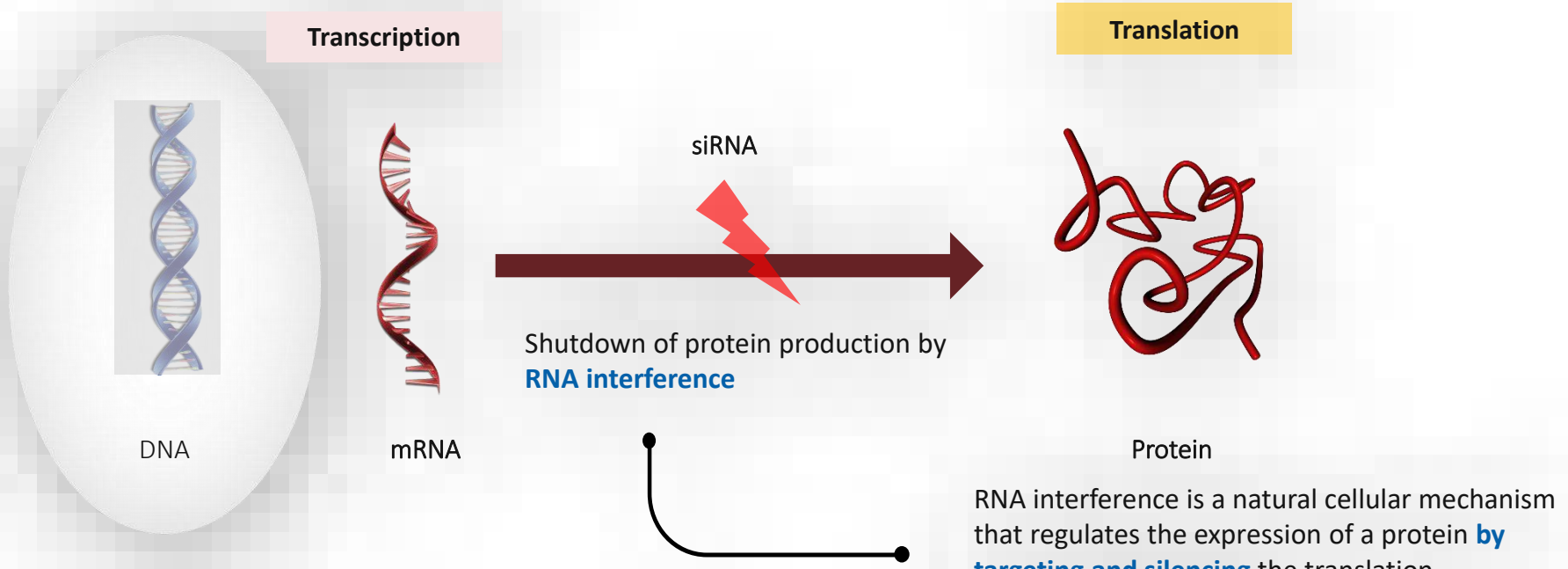
Synthetic siRNA targets a unique mRNA nucleotide sequence and can theoretically target any gene of interest[2]

[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 ?

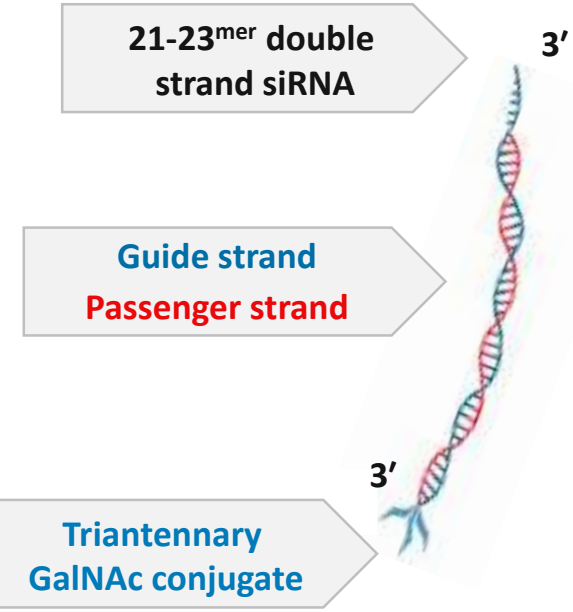
## Small interfering RNA

- 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**

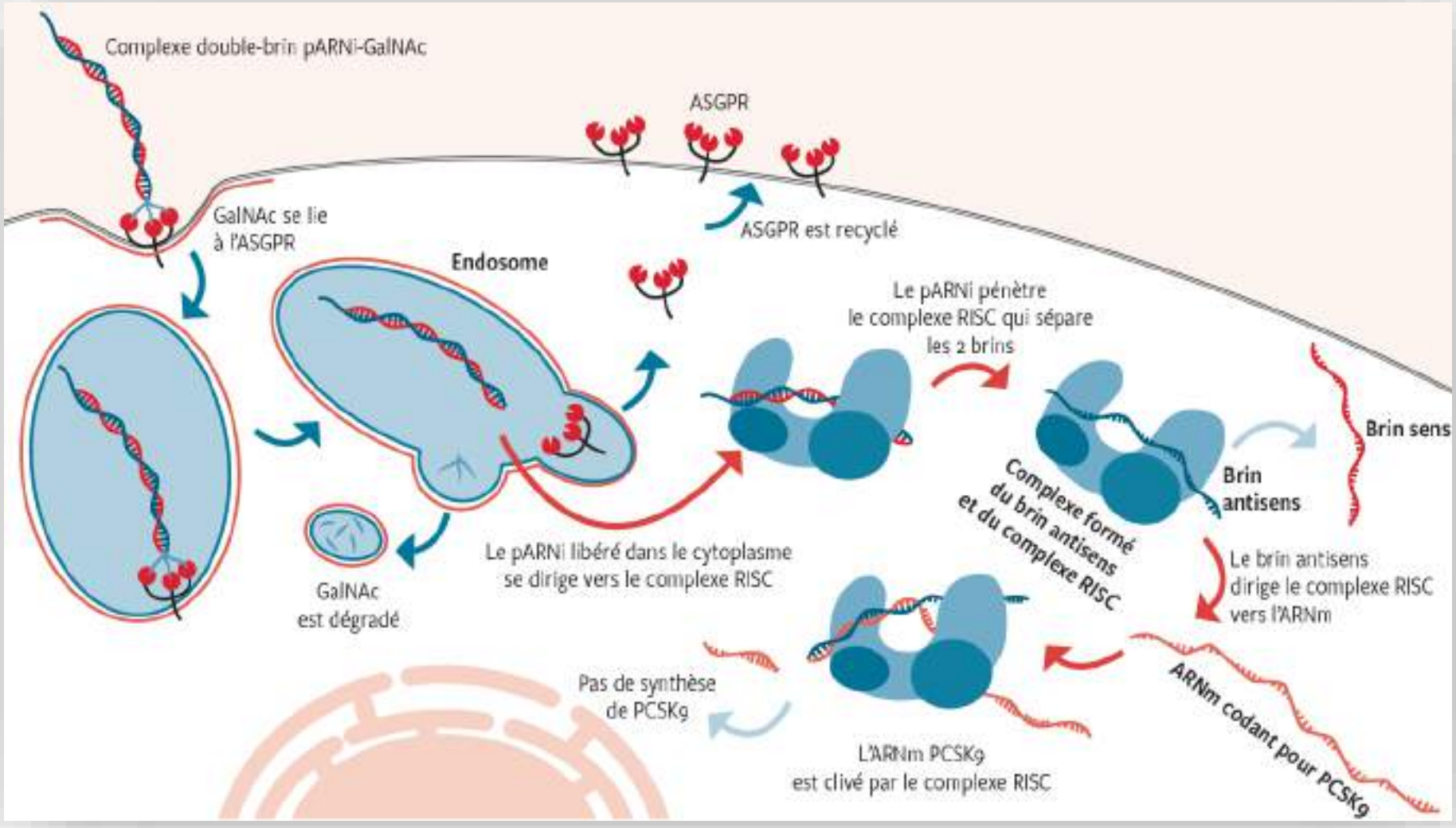
**Inclisiran**




[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

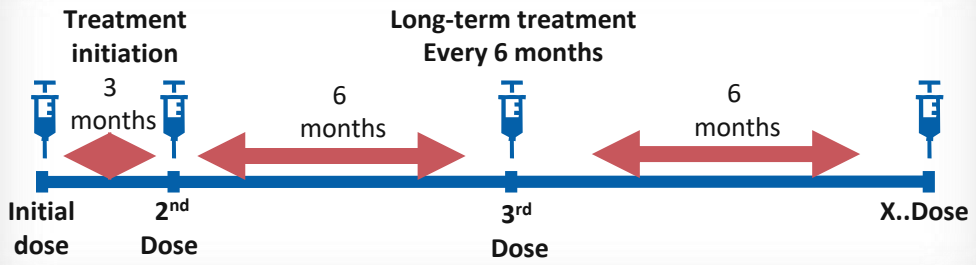
## Dose & administration

### Injection[1,2]

**1.5 mL solution per syringe**

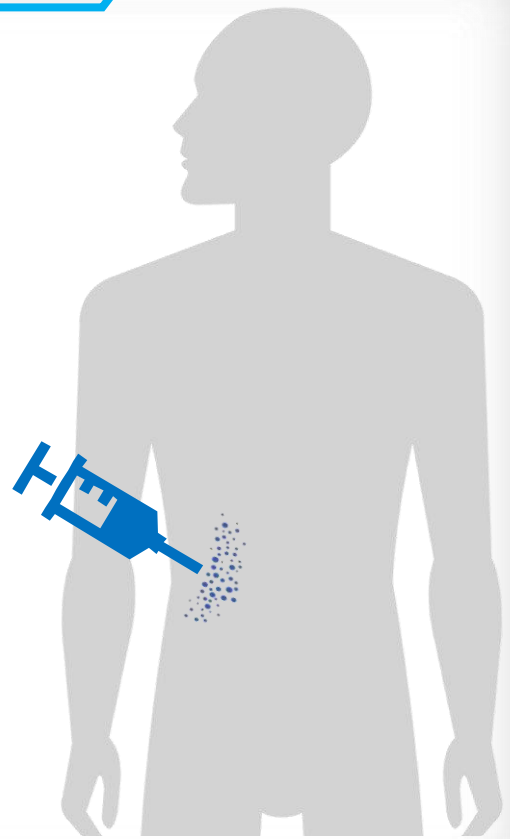
- 300 mg inclisiran sodium*
- Water as the diluent
- Sodium hydroxide and phosphoric acid (pH 7)
- Stored at room temperature

### 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] |
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| ORION-8 | III | 3700 | ASCVD or ASCVD RE or HFHe/HFHo | 36 mois | Baisse du LDL-C | NCT03814187 |
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| ORION-14 | I | 40 | Étude de recherche de dose | - | Baisse du LDL-C | NCT04774003 |
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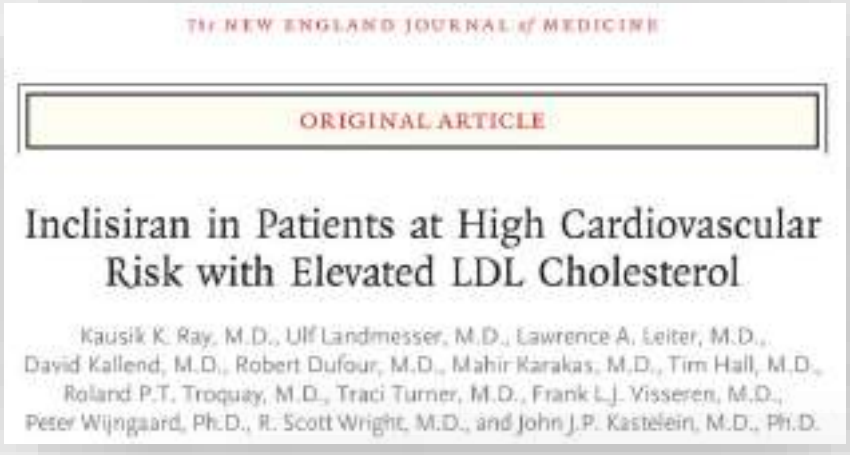
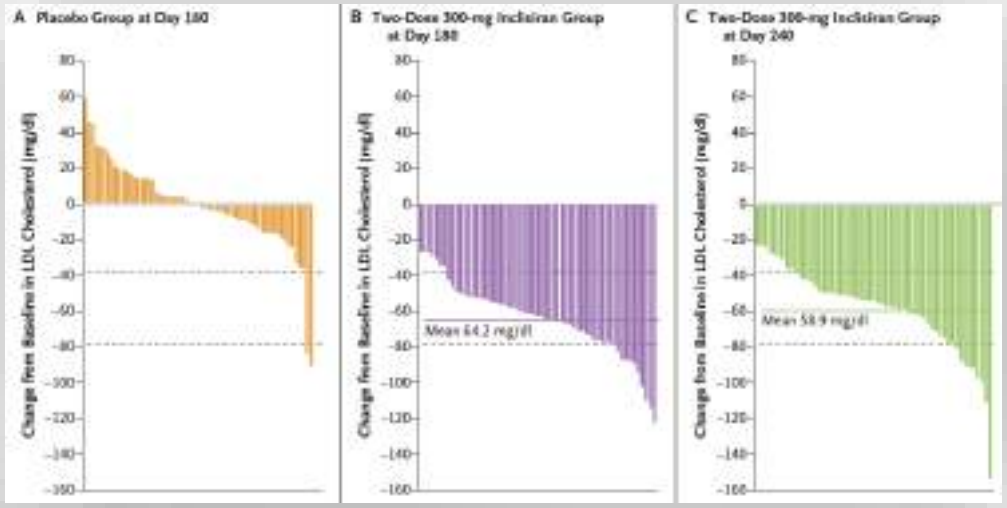
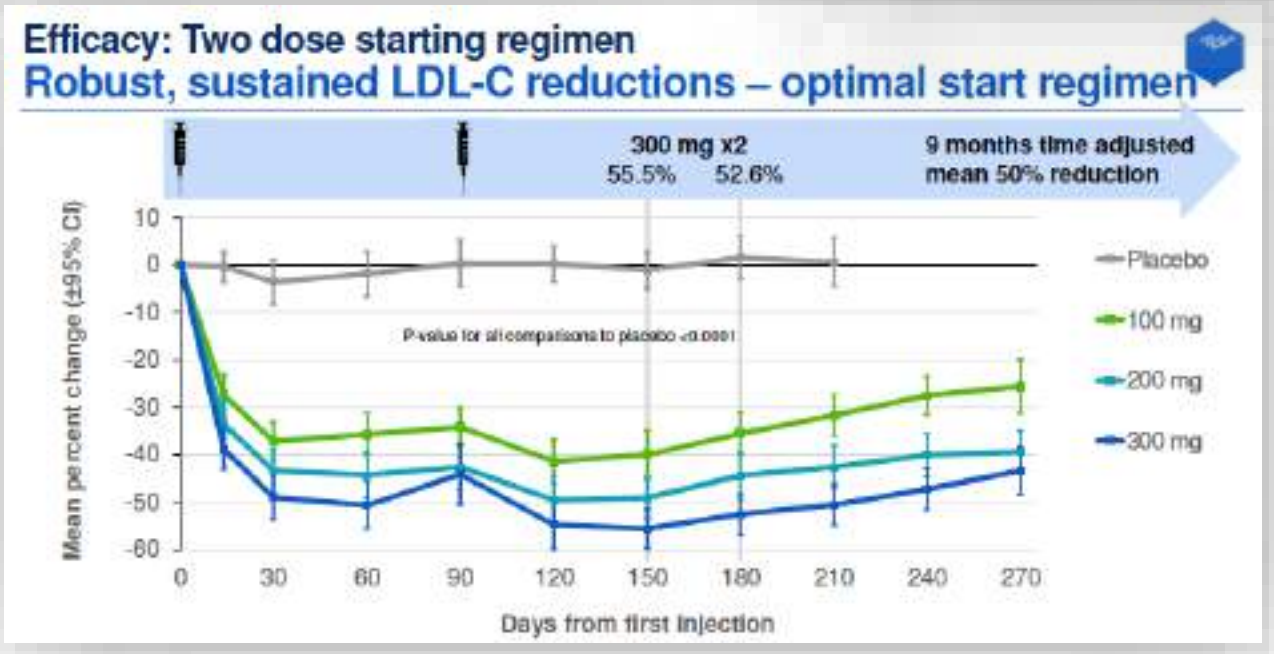
*Rev Med Suisse* 26 mai 2021;740:xxx

# Lowering PCSK9 with siPCSK9

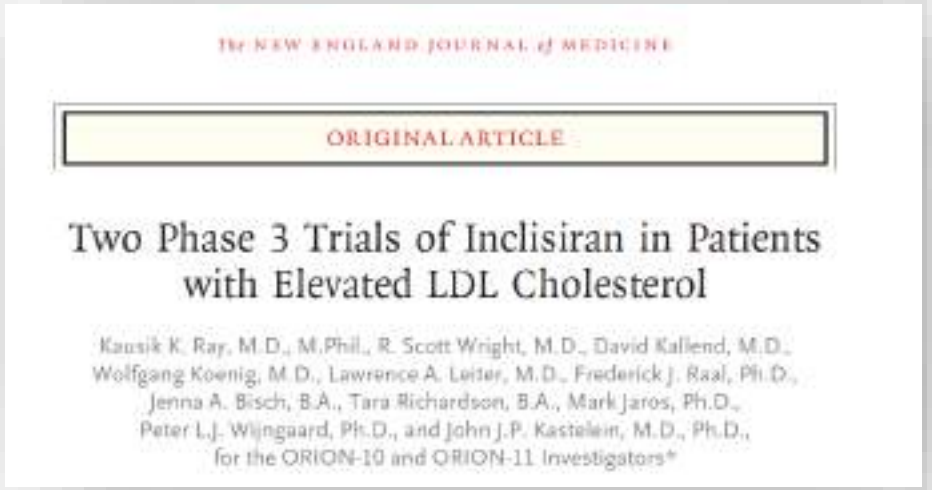



*New Engl J Med* 2017;376:1430

# Lowering PCSK9 with siPCSK9




**Efficacy and safety of Inclisiran vs placebo**

**in patients with very high cardiovascular risk,**

**with ASCVD or ASCVD-Risk Equivalent ***

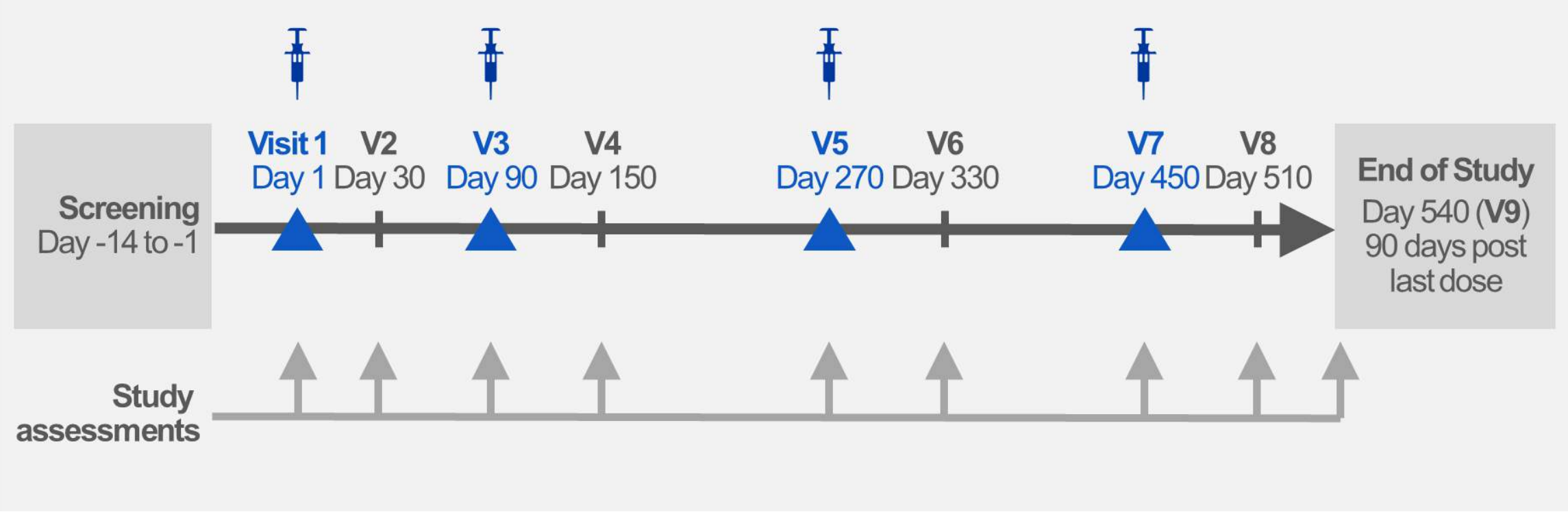
*Type-2 Diabetes, familial hypercholestereolemia or 10-year risk ≥20%

*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

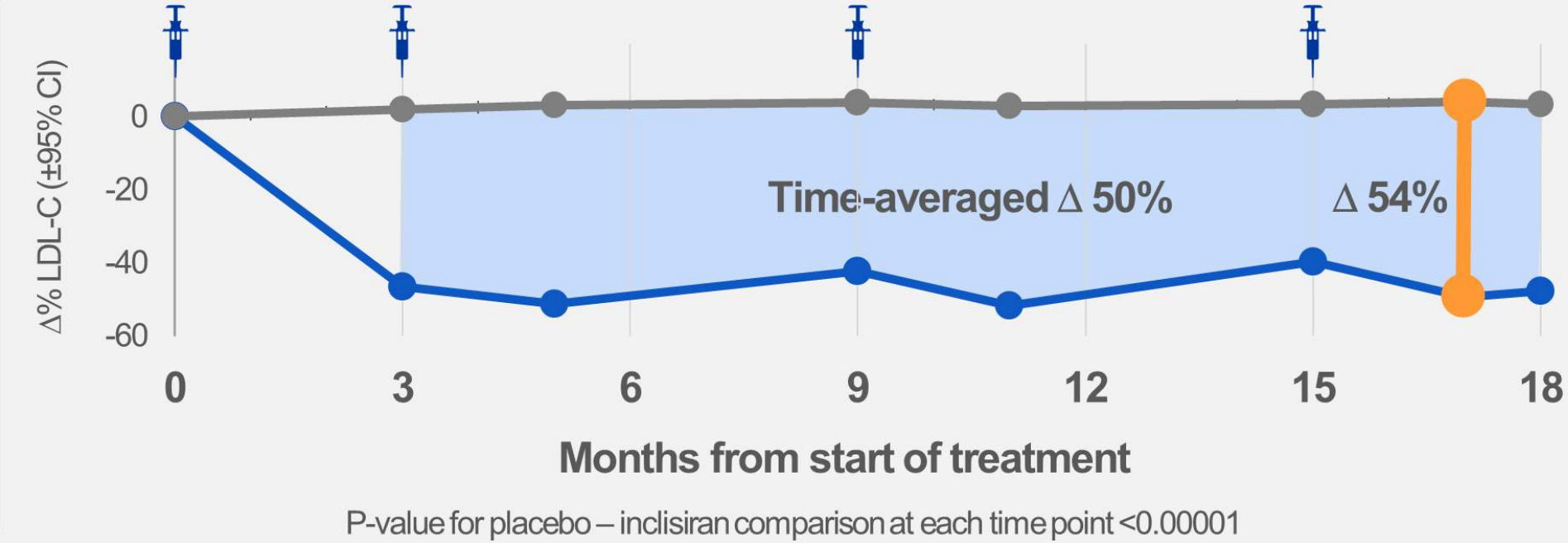



*New Engl J Med* 2020;382:1507

# ORION-11: Efficacy

## Durable, potent and consistent effect over 18 months

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

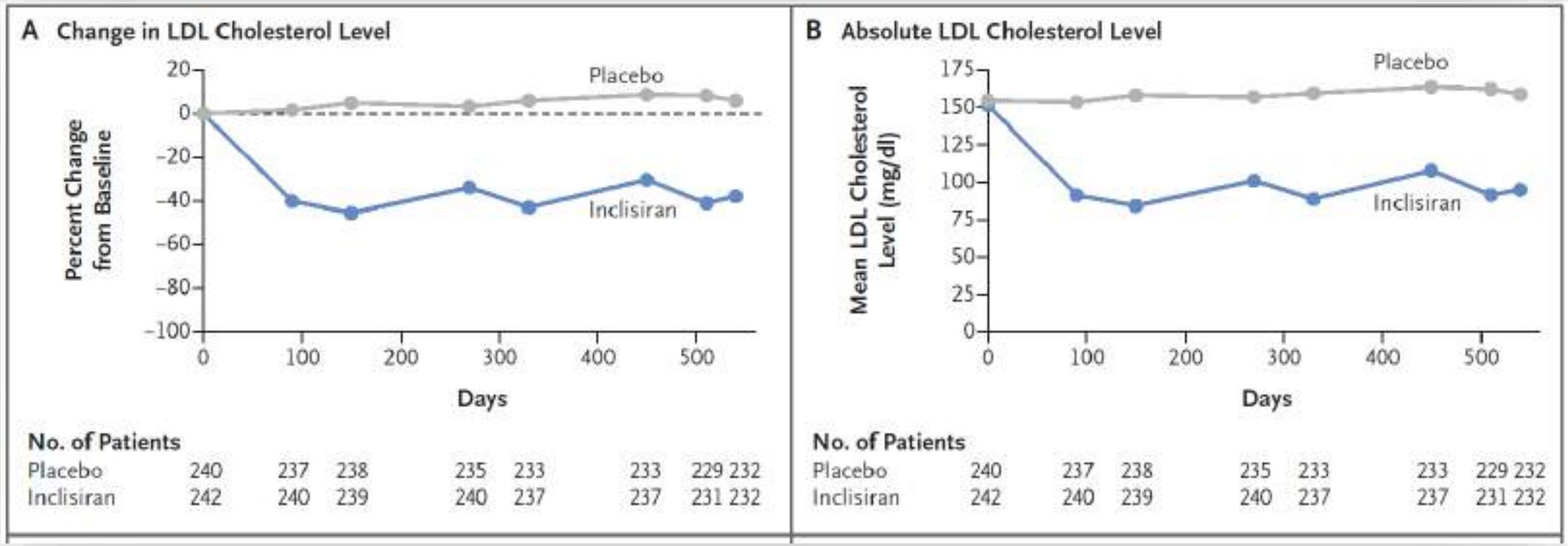



1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

*New Engl J Med* 2020;382:1507

# ORION-11: Efficacy

## Durable, potent and consistent effect over 18 months

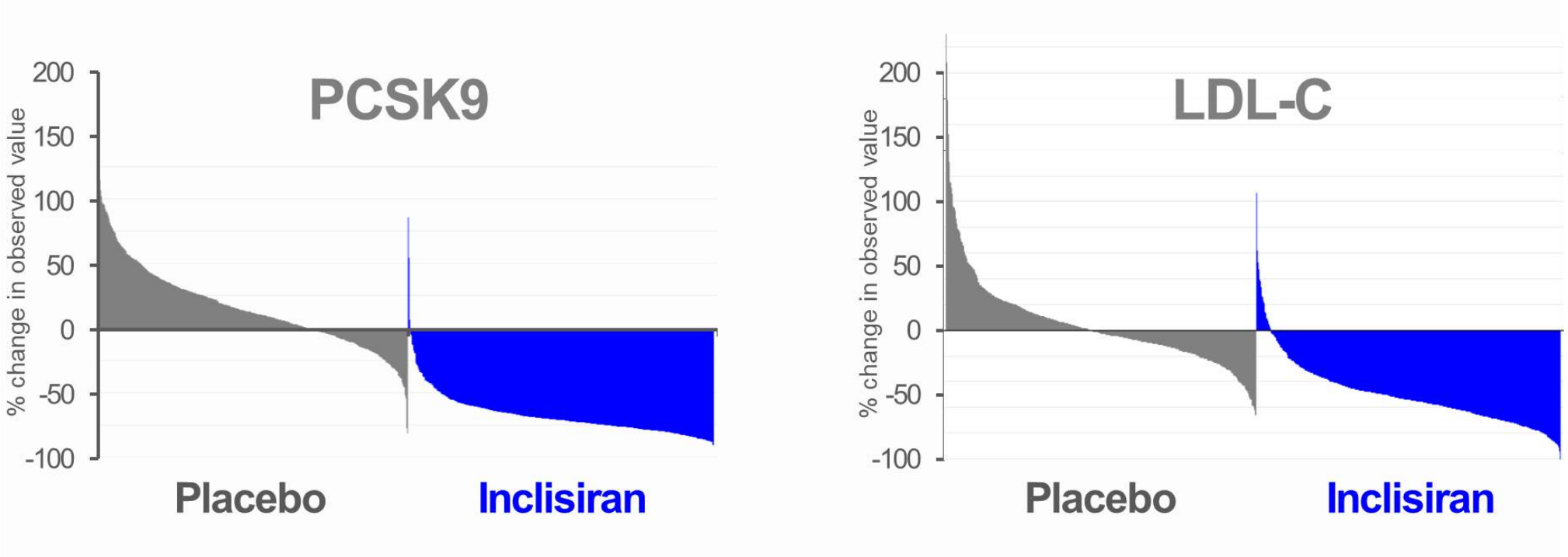



*New Engl J Med* 2020;382:1507

# ORION-11: Efficacy

## Potent, consistent response to inclisiran

**Individual patient responses contributing to primary endpoint – 17 months**

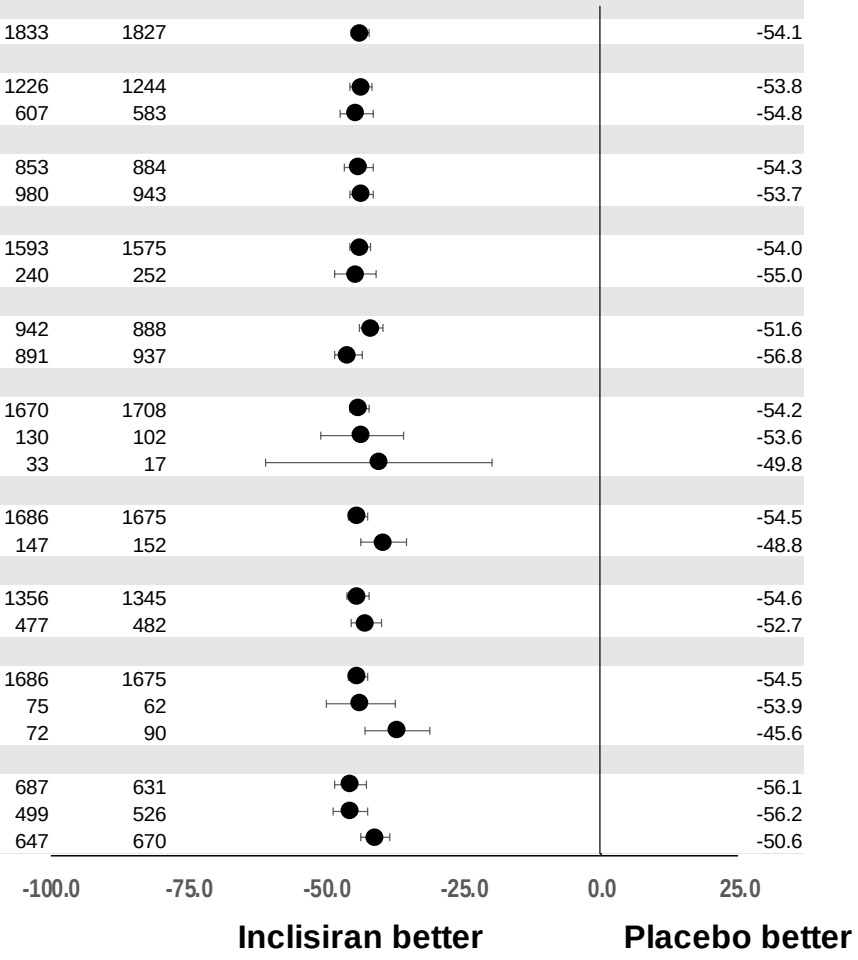



*New Engl J Med* 2020;382:1507

# 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**

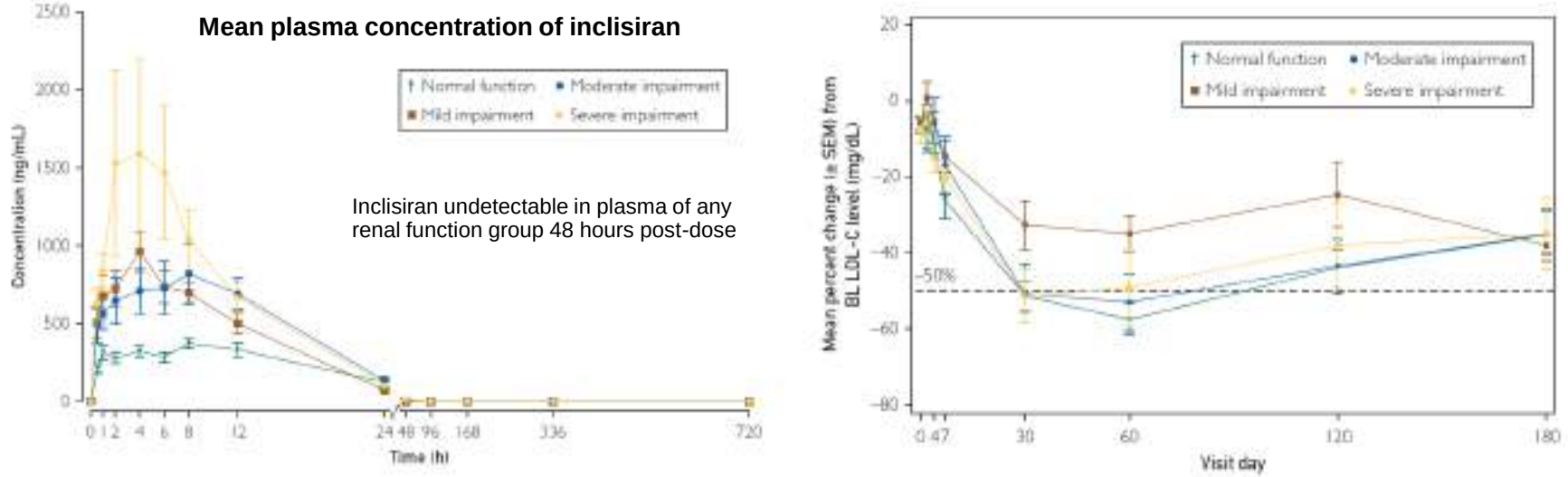
- Lends itself to routine clinical practice
- Enables provider control over medication adherence
- May offer patients meaningful new choices
- Offering safe, convenient and assured results

*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

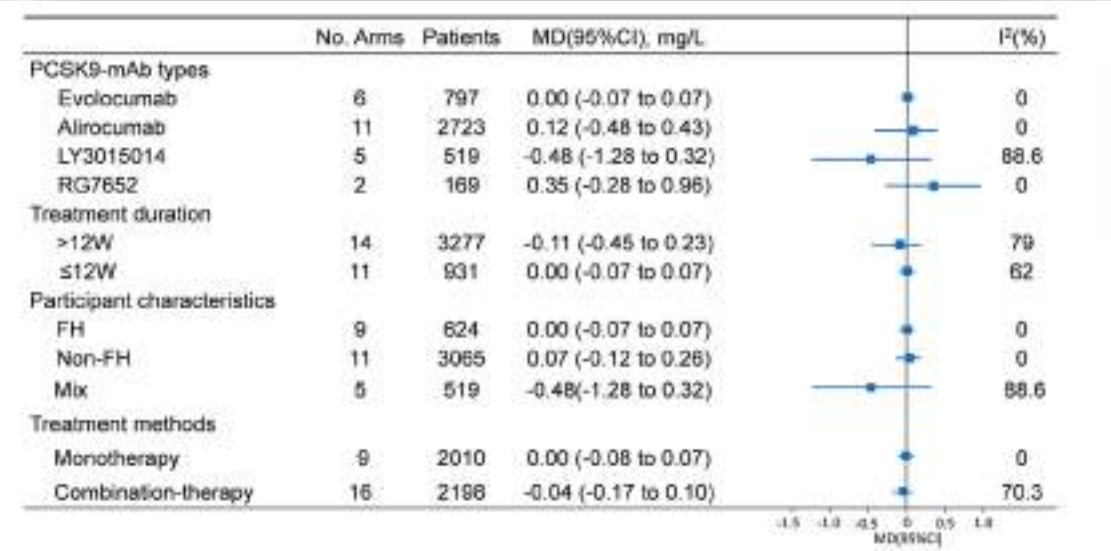
# PCSK9i and C-Reactive Protein

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 | I²(%) |
|---|---|---|---|---|
| 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

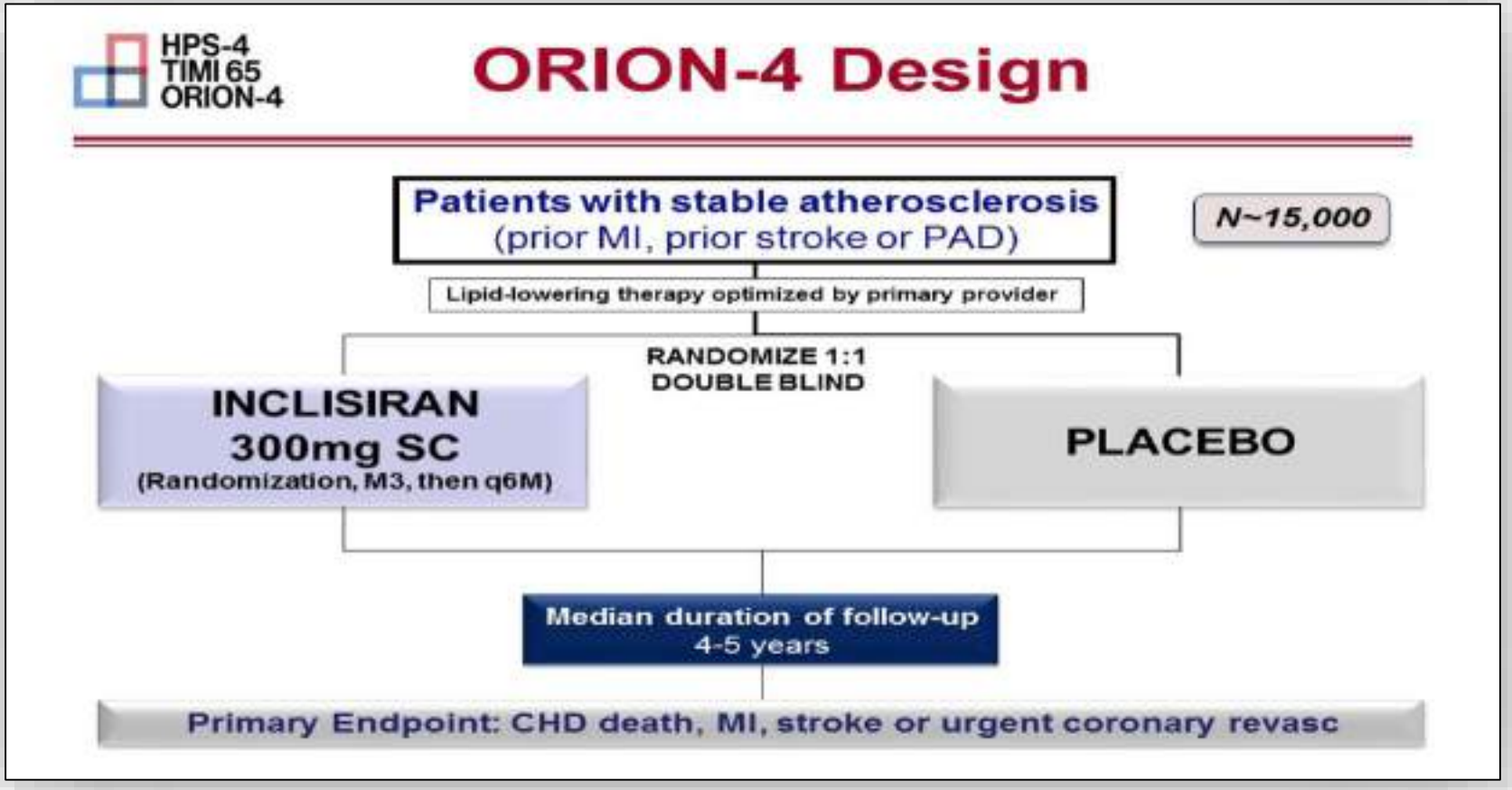
Yang Wang[1] · Jinsong Wang[1] · Shenming Wang[1]

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

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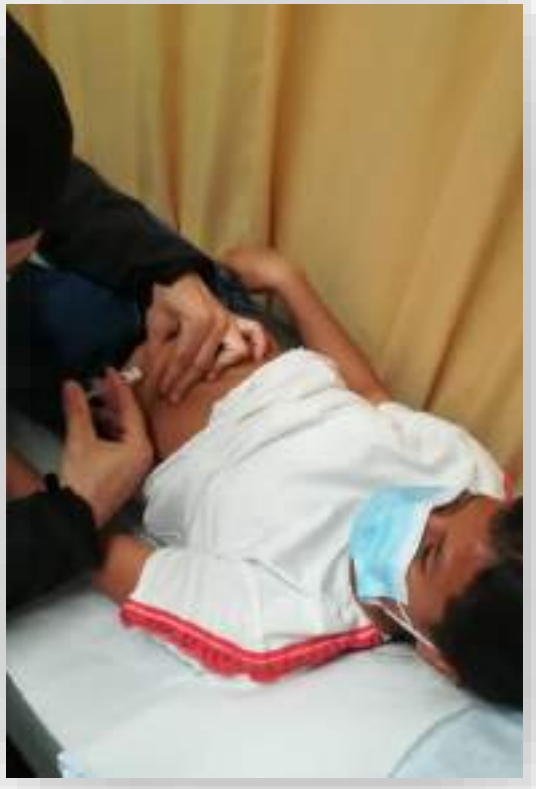


# The modern concept of lipid-lowering strategies to reduce cardiovascular diseases


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"*

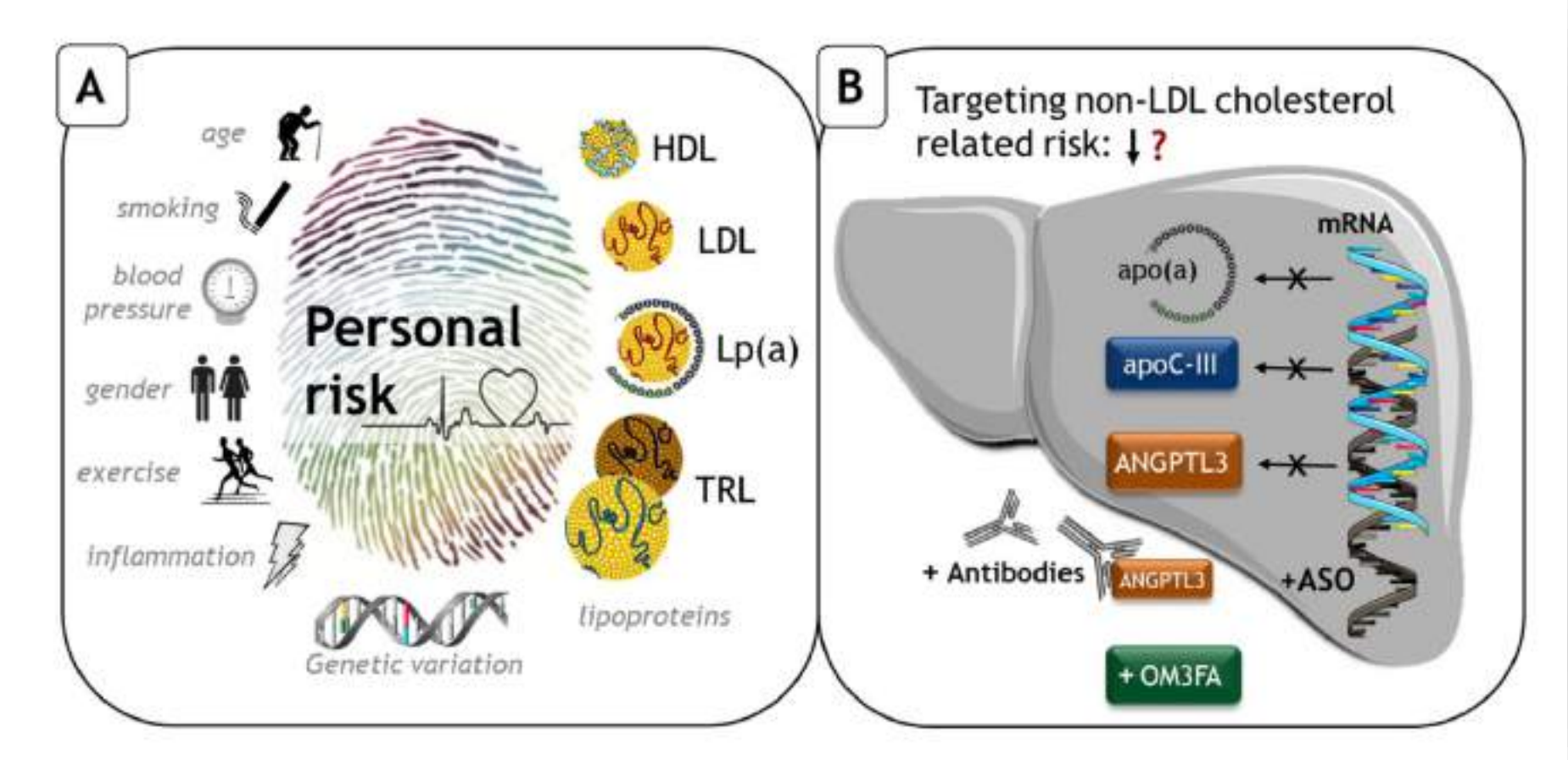
## Concept change III: Use lipid-lowering combination therapy

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

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

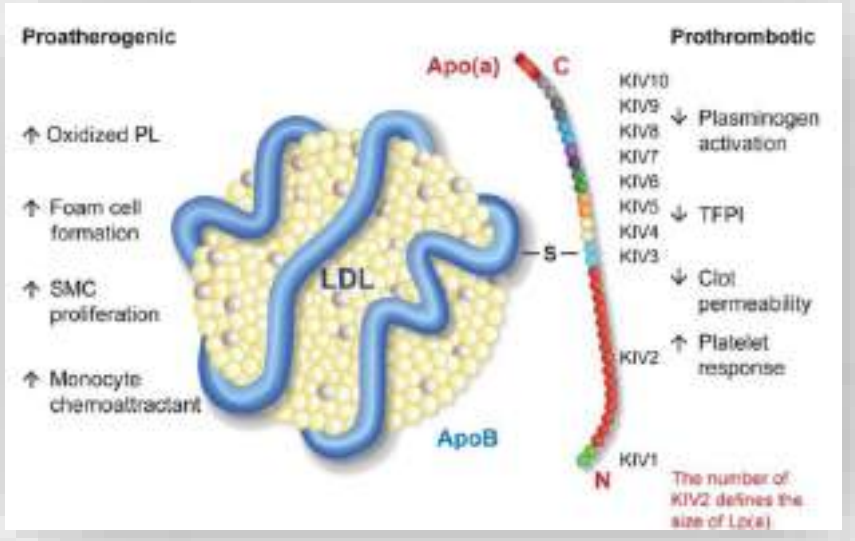
*Statin +/- ezetimibe + siRNA induced LDL-C lowering with great efficacy, safety and full treatment's adherence*

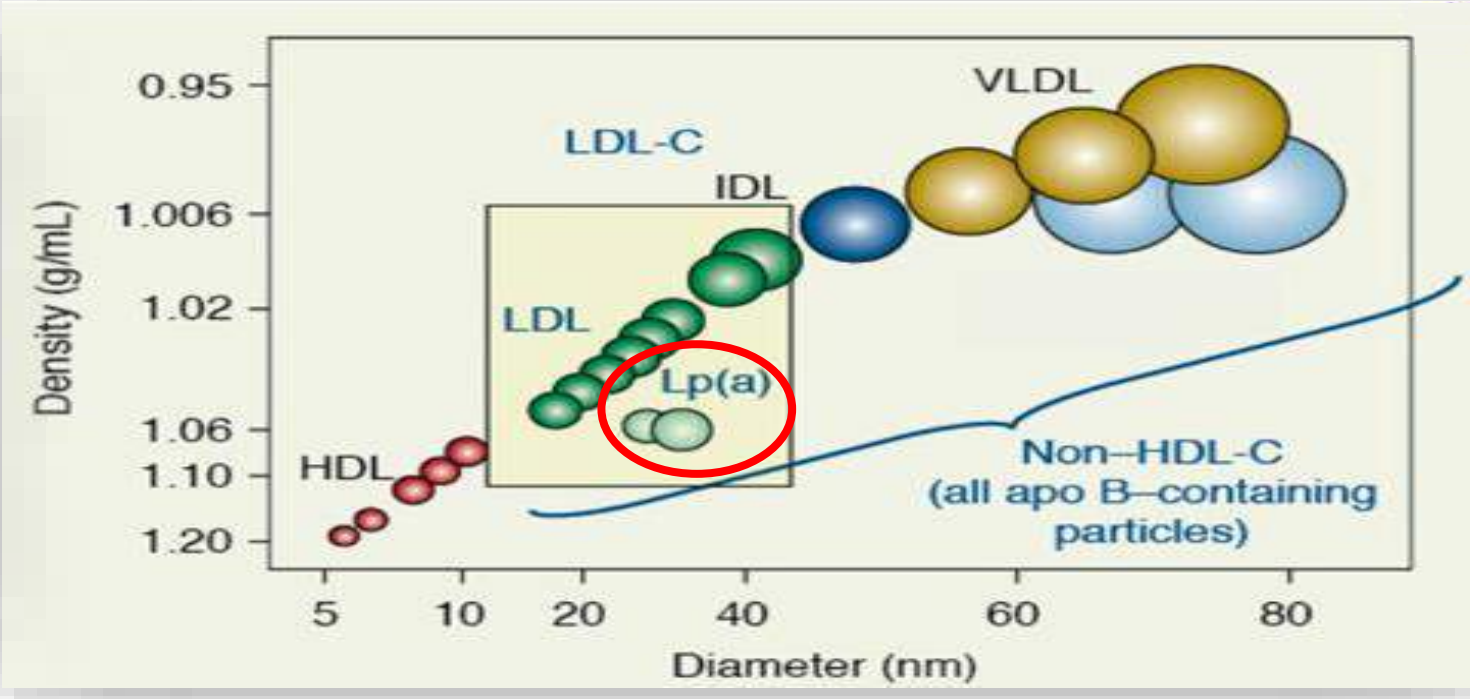
# Novel lipid lowering drugs: PCSK9 and beyond




*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/ehx023

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).

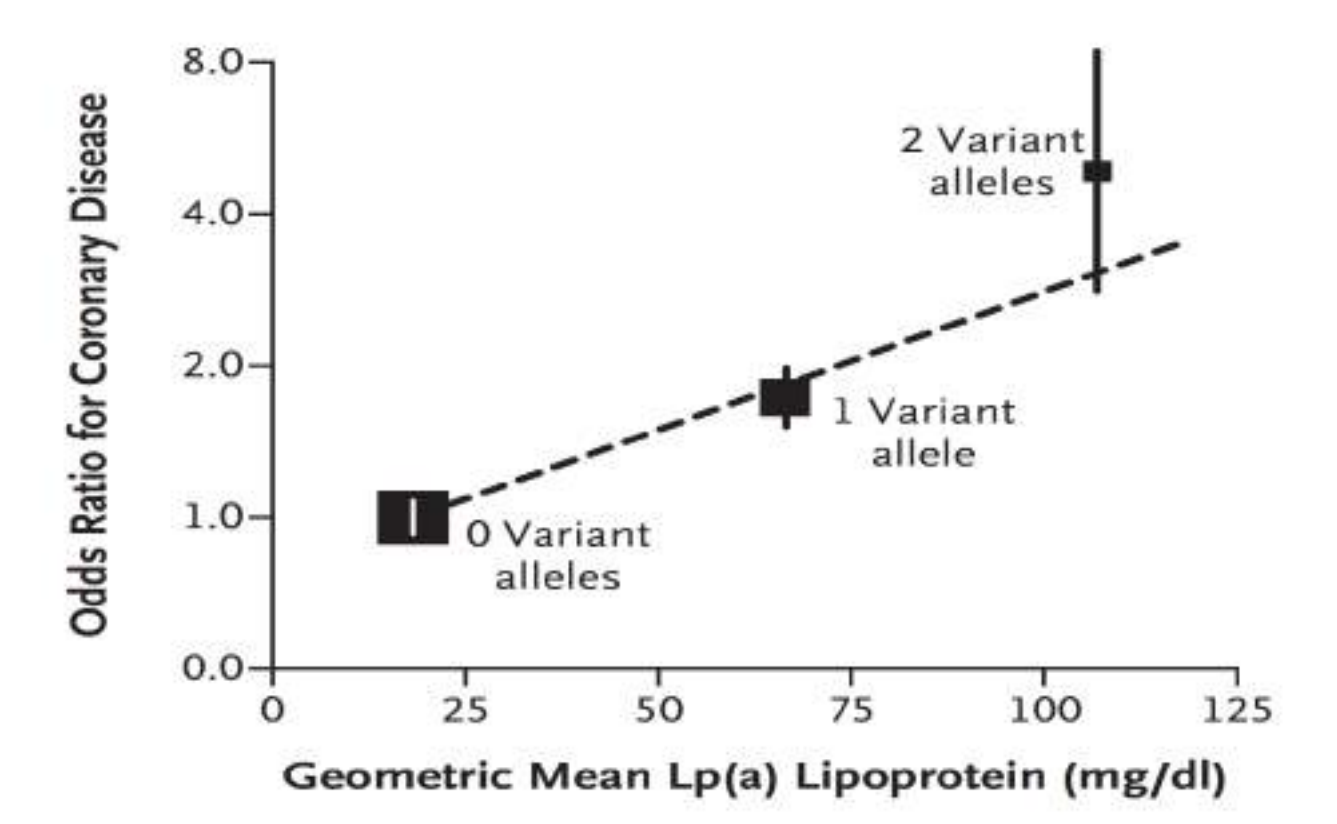
The 2019 ESC/EAS guidelines for the management of dyslipidaemia recommend to measure Lp(a) at least once in each adult person's lifetime.

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

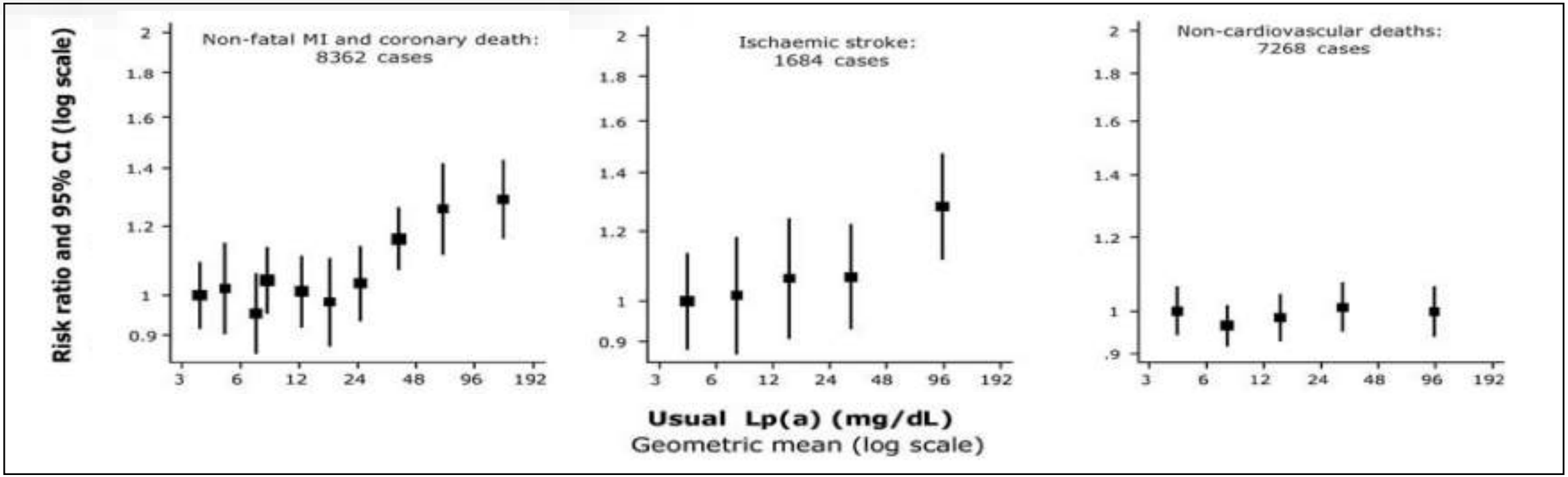
# Lipoprotein(a) and CV risk

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

CURRENT OPINION

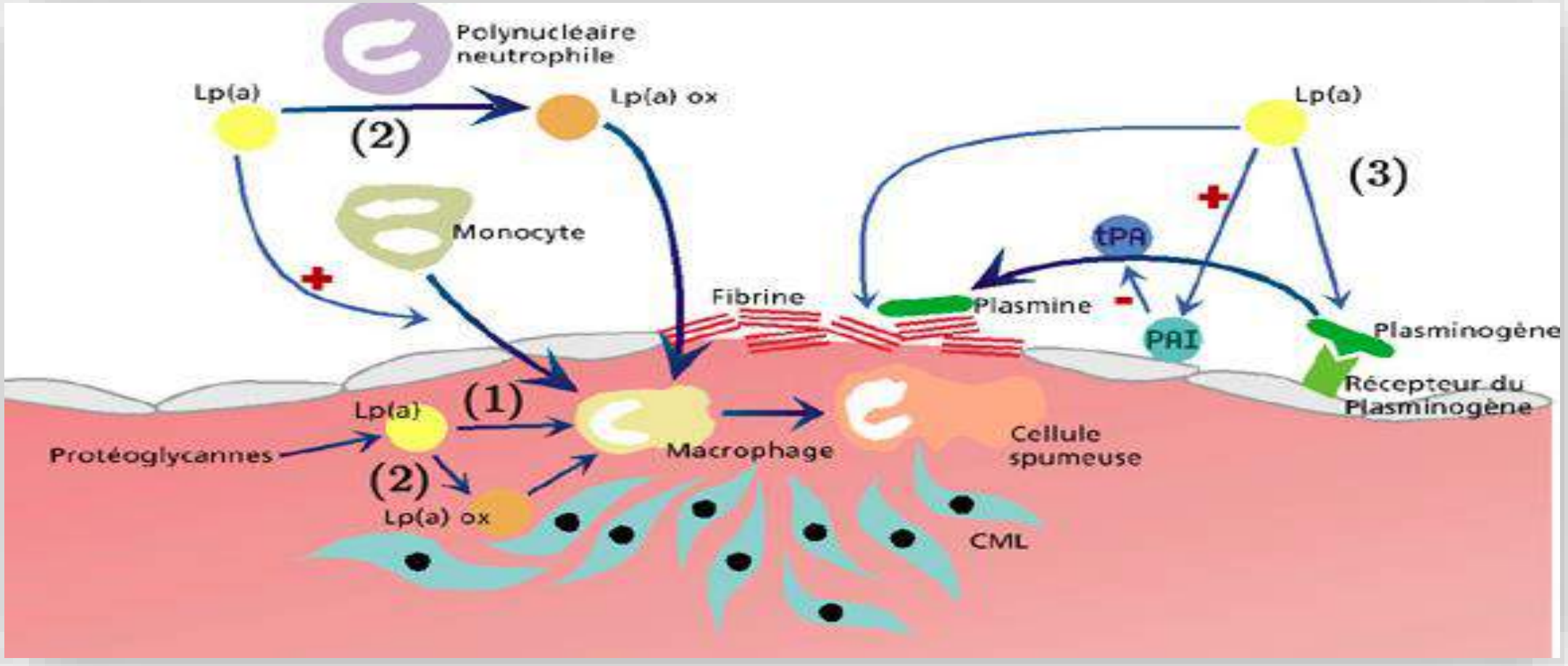
## Lipoprotein(a) as a cardiovascular risk factor: current status

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 |

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)

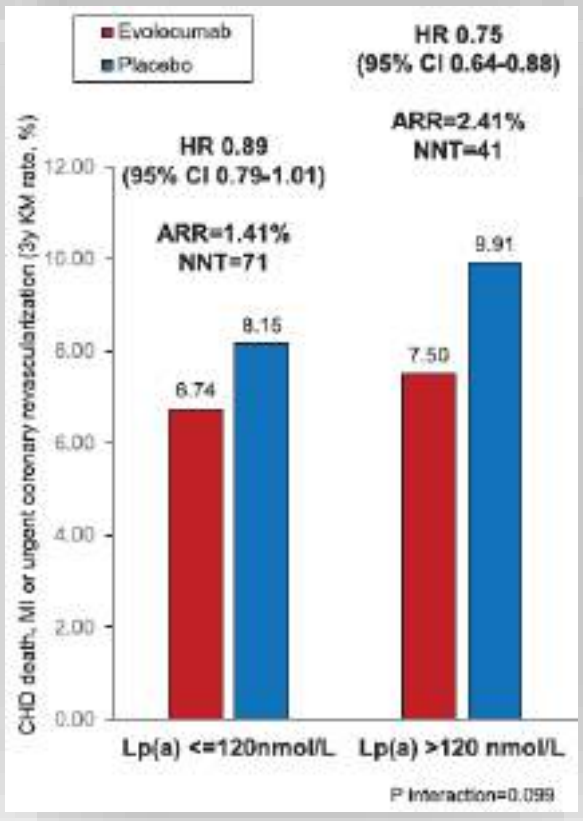
# PCSK9 mAb - Lp(a) and CV outcomes ?

Circulation

ORIGINAL RESEARCH ARTICLE

**Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk**

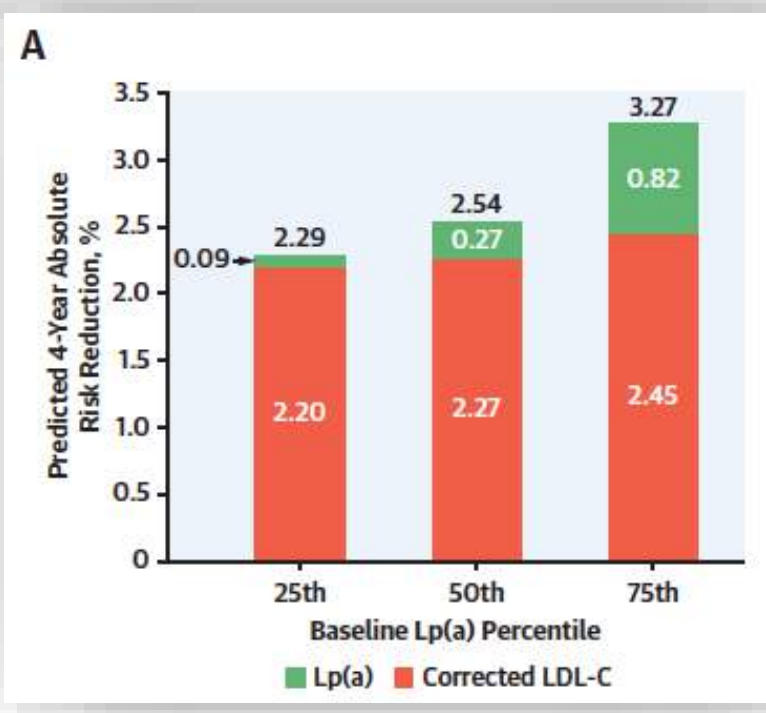
Insights From the FOURIER Trial




*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**

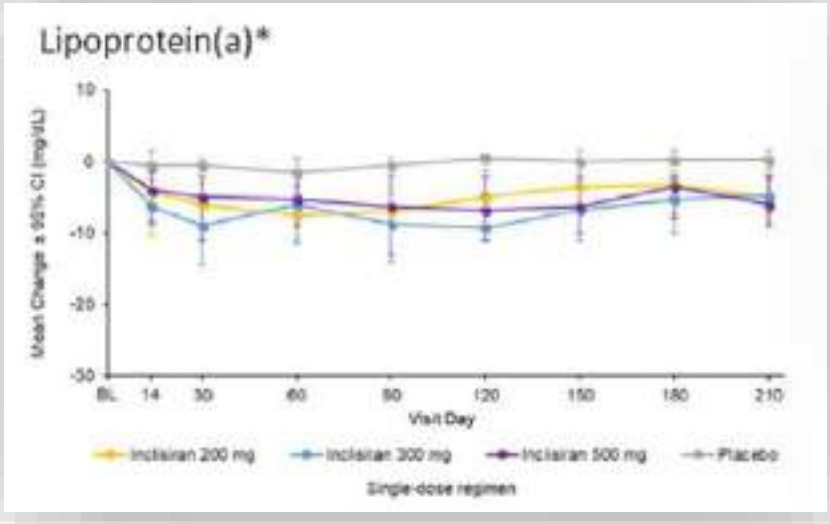



Table 2. Lipids and Lipoproteins at Baseline and Day 180*

| | 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 (70.88) | 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

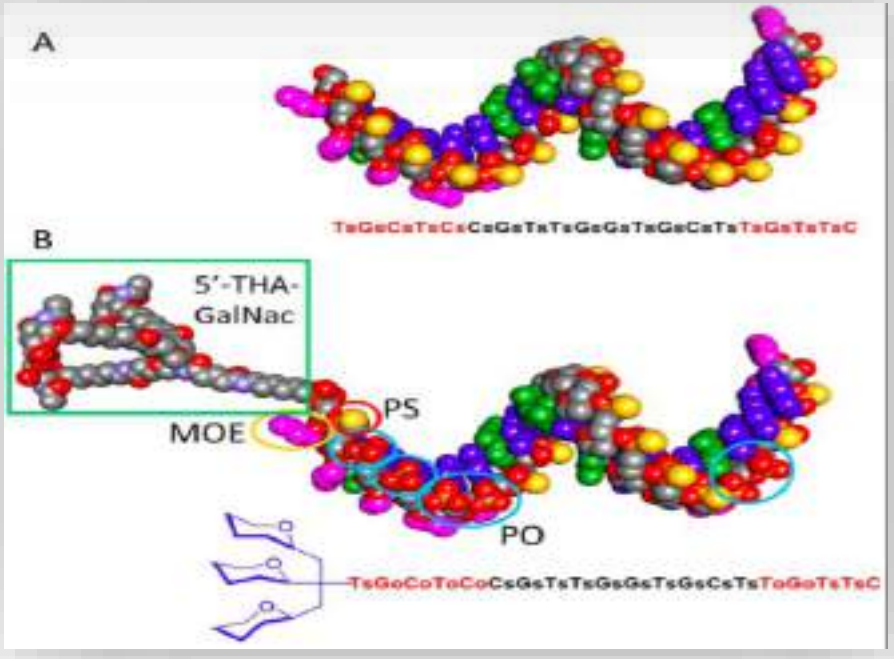
# Lowering Lipoprotein(a) with apo(a)-antisense

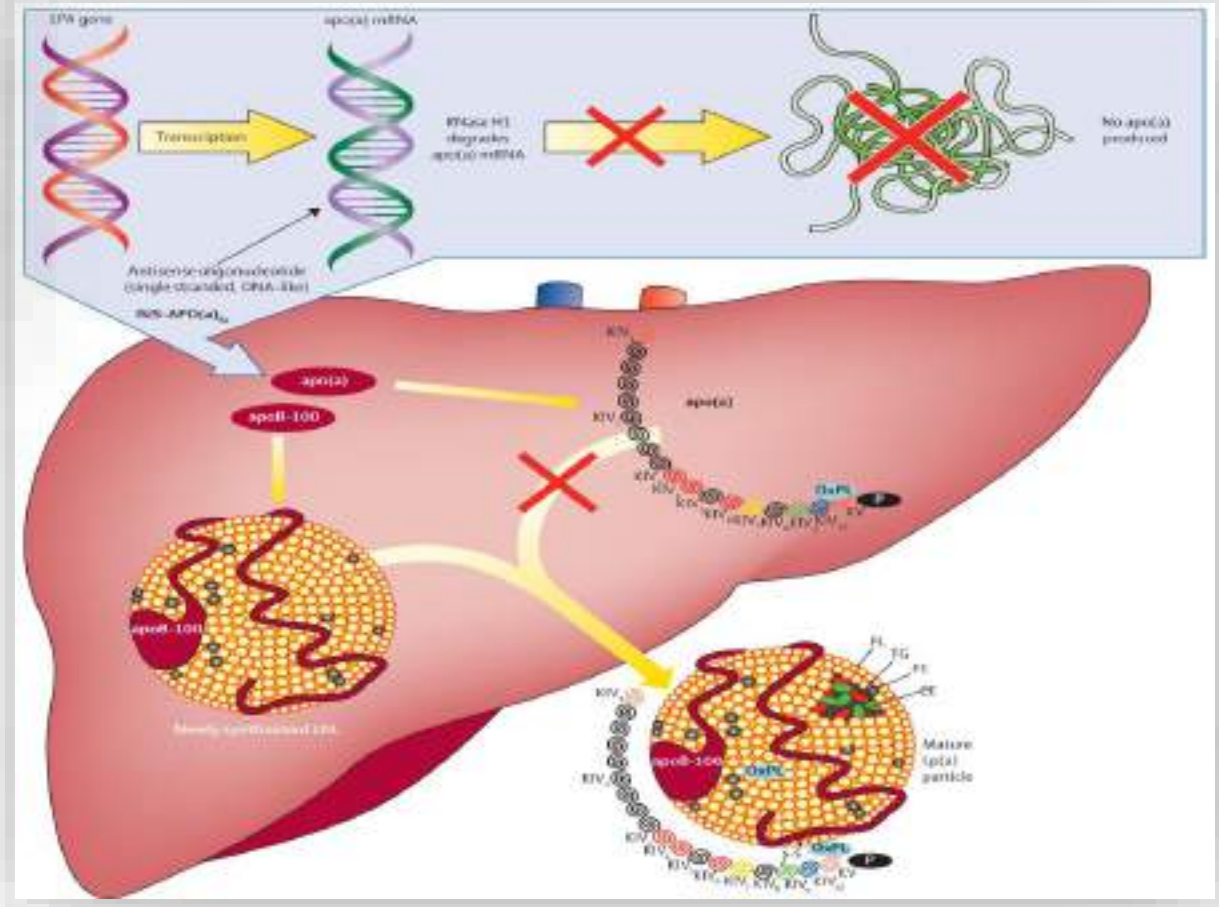
**Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study**

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, Roxie 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

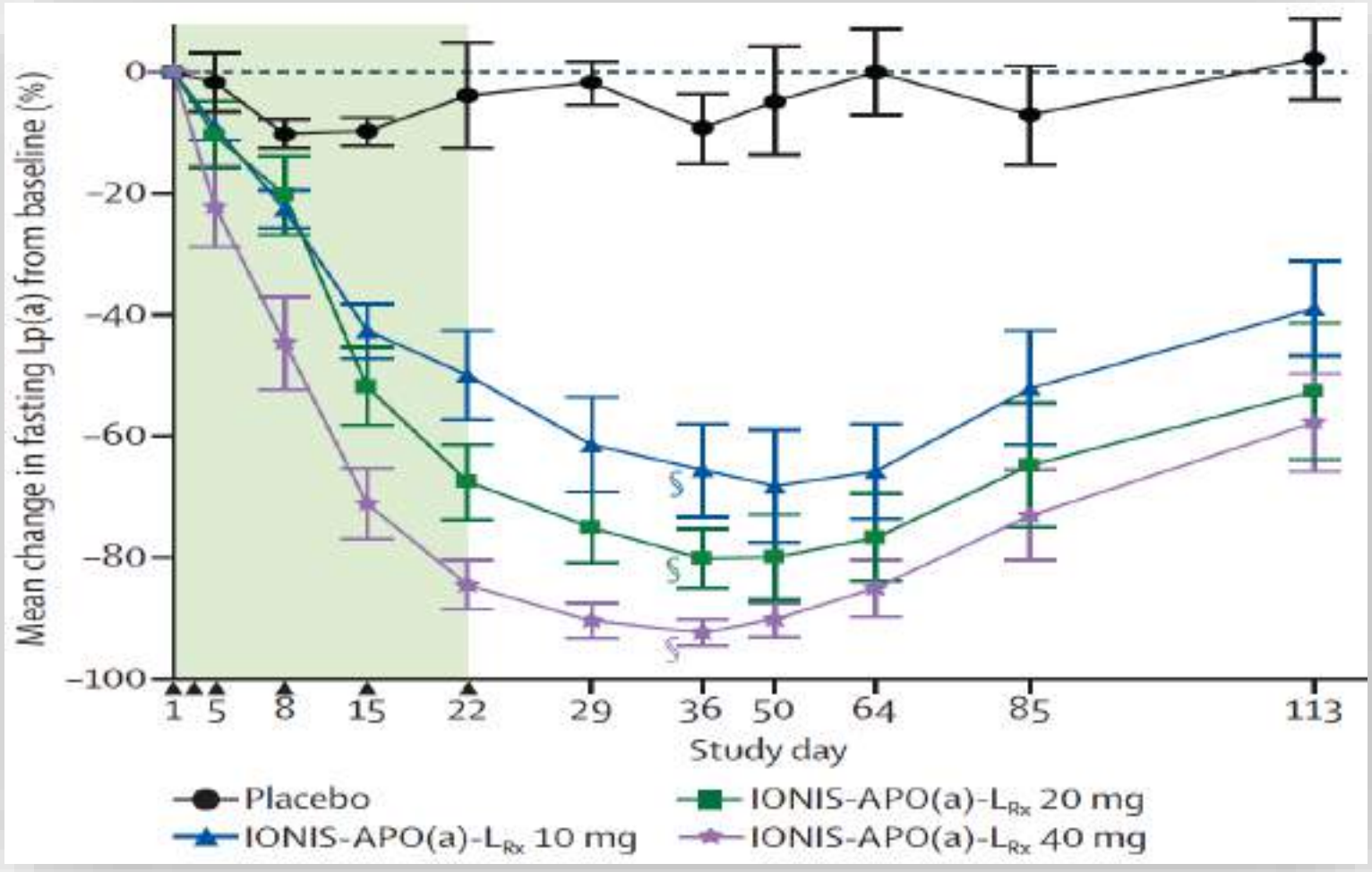



*Lancet* 2015;386:1472

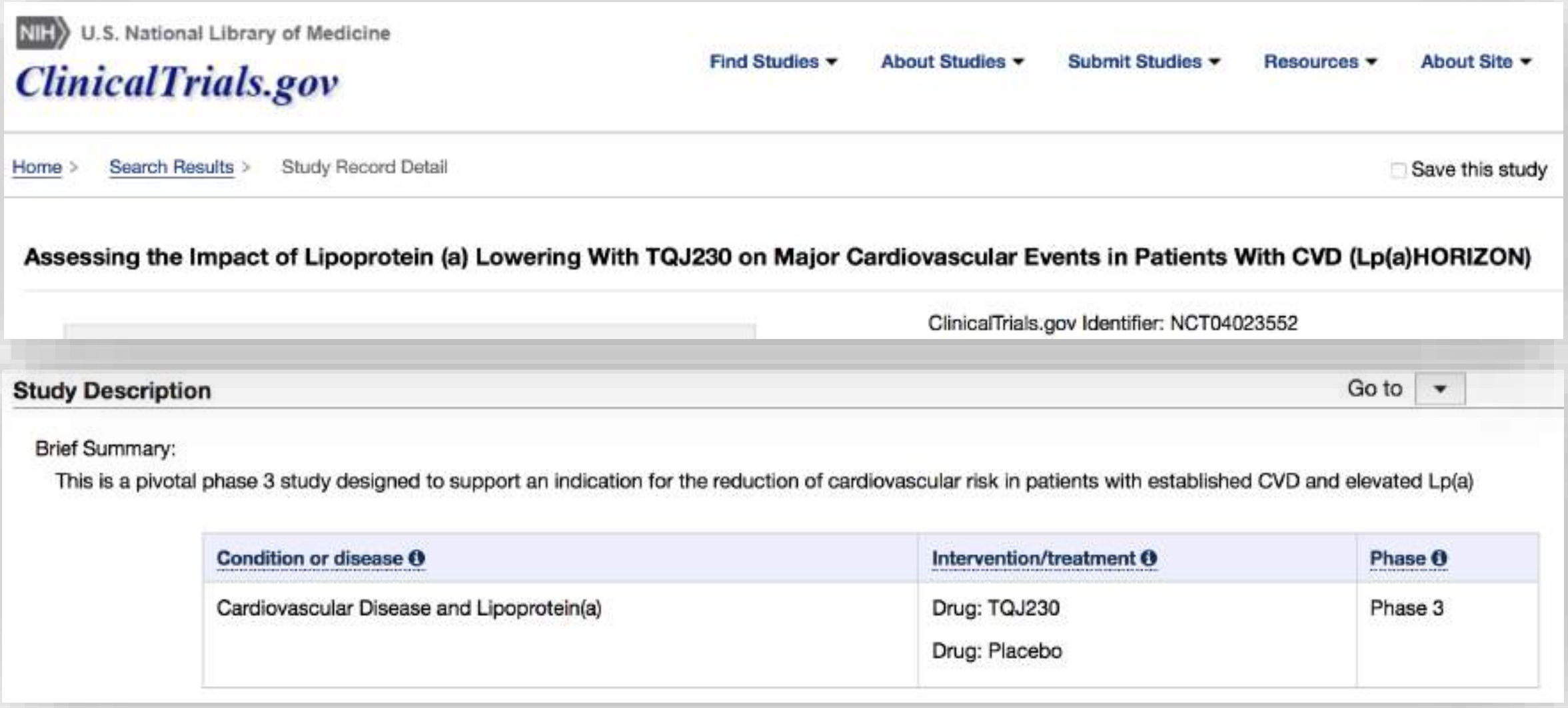
# Lowering Lipoprotein(a) with apo(a)-antisense

Effect of Galnac apo(a) antisense




*Lancet* 2016;388:2239

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



U.S. National Library of Medicine

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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<br>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] Helmo Kassahun,[9] Gerald F Watts[12,13]**

[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]DPS MIRA, 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

## Background & Objective

- Lipoprotein(a) [Lp(a)] is a risk factor for myocardial infarction and other atherosclerotic events[1,2]
- No approved medicines selectively target Lp(a) and lower cardiovascular risk in clinically-relevant 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 <180 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


## Disclosures & Acknowledgements

[illegible]

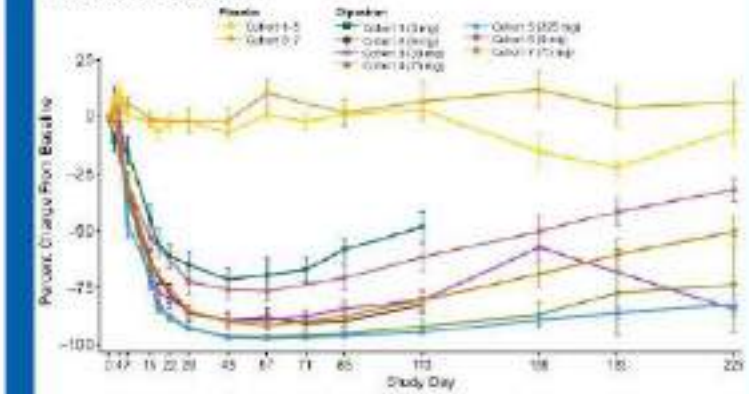
During the treatment period, one dose of olpasiran:

- 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 <180 nmol/L | | Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L | |
|---|---|---|---|---|
| | Placebo (N=12) | Olpasiran (N=30) | Placebo (N=6) | Olpasiran (N=14) |
| Any AE | 5 (41.7) | 12 (40.0) | 4 (66.7) | 10 (71.4) |
| Serious AE | 2 | 3 | 1 (16.7) | 1 |
| AEs occurring in more than one subject across cohorts | | | | |
| Headache | 1 (8.3) | 0 | 1 (16.7) | 3 (21.4) |
| Upper respiratory tract infection | 1 (8.3) | 4 (13.3) | 1 (16.7) | 2 (14.3) |
| Back pain | 1 (8.3) | 1 (3.3) | 0 | 3 (21.4) |
| Nasopharyngitis | 1 (8.3) | 1 (3.3) | 1 (16.7) | 1 |
| Viral upper respiratory tract infection | 1 | 1 (3.3) | 0 | 2 (14.3) |
| Blood creatine phosphokinase increased | 1 (8.3) | 1 (3.3) | 0 | 1 |
| Contusion | 1 | 1 (3.3) | 1 | 1 (7.1) |
| Skin abrasion | 1 | 1 (3.3) | 0 | 1 (7.1) |
| Fatigue | 1 | 0 | 1 (16.7) | 1 (7.1) |
| Arthralgia | 1 | 1 (3.3) | 0 | 1 (7.1) |
| Epistaxis | 1 (8.3) | 1 | 1 (16.7) | 1 |
| AEs of possible interest | | | | |
| Injection site reaction | 1 | 1 (3.3) | 0 | 1 |

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




Presented at [illegible], November 13–17, 2020



## Results

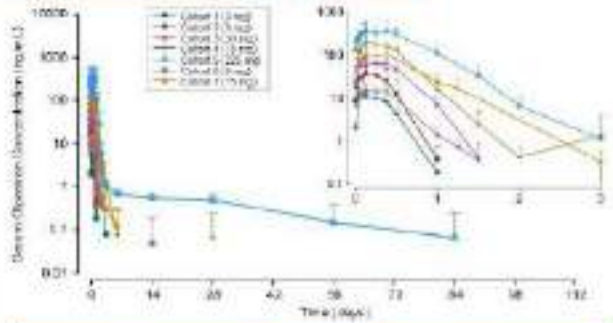
**Table 2. Baseline Characteristics**

| Baseline Characteristic | | Cohorts 1–5 Screening Lp(a) 70 to <180 nmol/L | | Cohorts 6 & 7 Screening Lp(a) ≥200 nmol/L | |
|---|---|---|---|---|---|
| | | Placebo (N=12) | Olpasiran (N=30) | Placebo (N=6) | Olpasiran (N=14) |
| Age (years), mean (SD) | | 49.2 (9.3) | 49.8 (10.3) | 57.5 (9.3) | 53.7 (9.4) |
| Women, n (%) | | 7 (58.3) | 18 (60.0) | 4 (66.7) | 8 (57.1) |
| Ethnicity, n (%) | Hispanic/Latino | 5 (41.7) | 10 (33.3) | 1 (16.7) | 4 (28.6) |
| | Not Hispanic/Latino | 7 (58.3) | 20 (66.7) | 5 (83.3) | 10 (71.4) |
| Race, n (%) | Black | 2 (16.7) | 3 (10.0) | 0 | 1 (7.1) |
| | White | 7 (58.3) | 21 (70.0) | 5 (83.3) | 13 (92.9) |
| | Other | 3 | 6 | 1 (16.7) | 0 |
| BMI (kg/m²), mean (SD) | | 27.8 (3.5) | 27.0 (3.5) | 28.1 (2.1) | 27.7 (2.2) |
| Lp(a) (nmol/L), median (Q1, Q3) | | 124 (104, 157) | 122 (97, 146) | 272 (233, 307) | 241 (224, 314) |

### 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 estimated from serum within 2 to 3 days
- Olpasiran AUC exposures in subjects with Lp(a) ≥200 nmol/L (Cohorts 6 and 7) were 18–39% lower than in subjects with Lp(a) >70 to <180 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

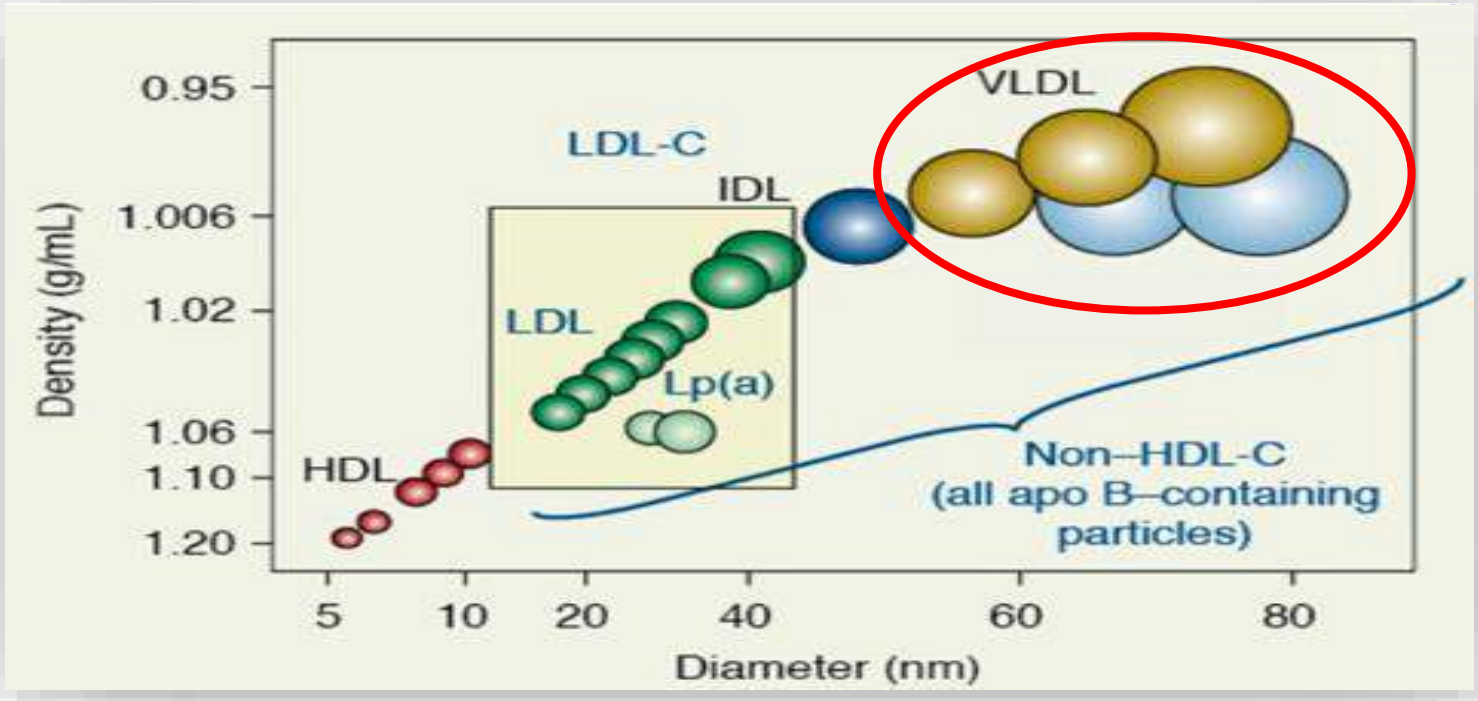
- No safety concerns were identified for olpasiran in this single dose study
  - No clinically relevant changes in liver tests, platelets or coagulation parameters, or renal function were observed
- Systemic exposures of olpasiran increased approximately dose-proportionally
- In adults with elevated 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 50% of baseline Lp(a)
- These results validate the approach of using 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. [illegible]
2. Nissen SE, et al. *N Engl J Med* 2019;380:2307–18.

# Characteristics of lipoproteins

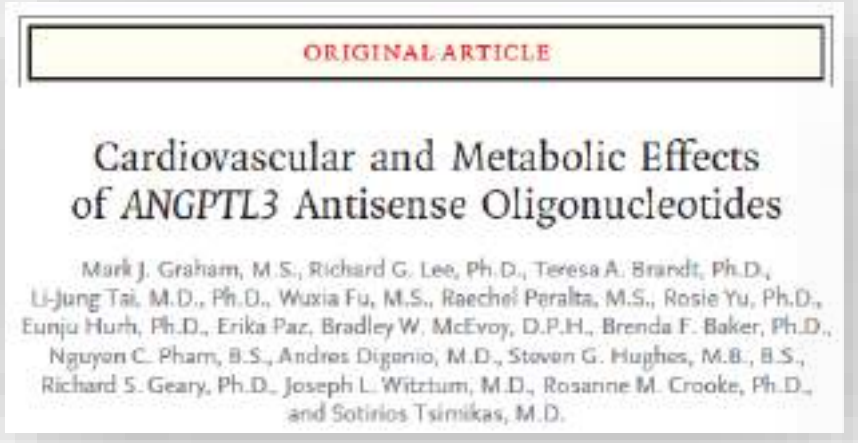
Remnants cholesterol



# 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.***

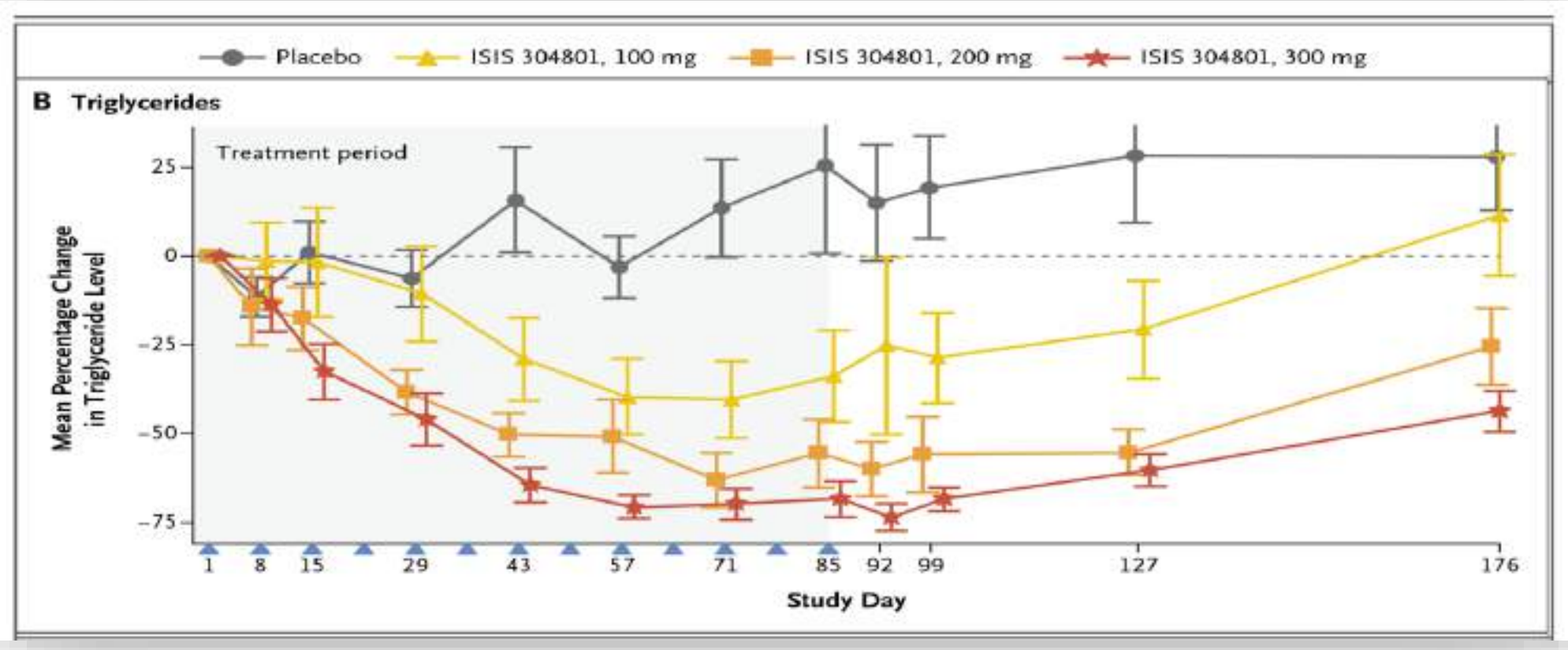
| Measure | Placebo (N=8) | ANGPTL3-$L_{Rx}$ | | | |
|---|---|---|---|---|---|
| | | 10 mg (N=6) | 20 mg (N=5) | 40 mg (N=6) | 60 mg (N=6) |
| ANGPTL3 — ng/ml | 132.5±38.9 | 45.3±22.9† | 24.5±7.5† | 21.1±5.0† | 16.6±8.1† |
| Triglycerides — mg/dl | 183±76 | 135±55 | 73±20† | 93±24‡ | 82±27† |
| LDL cholesterol — 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

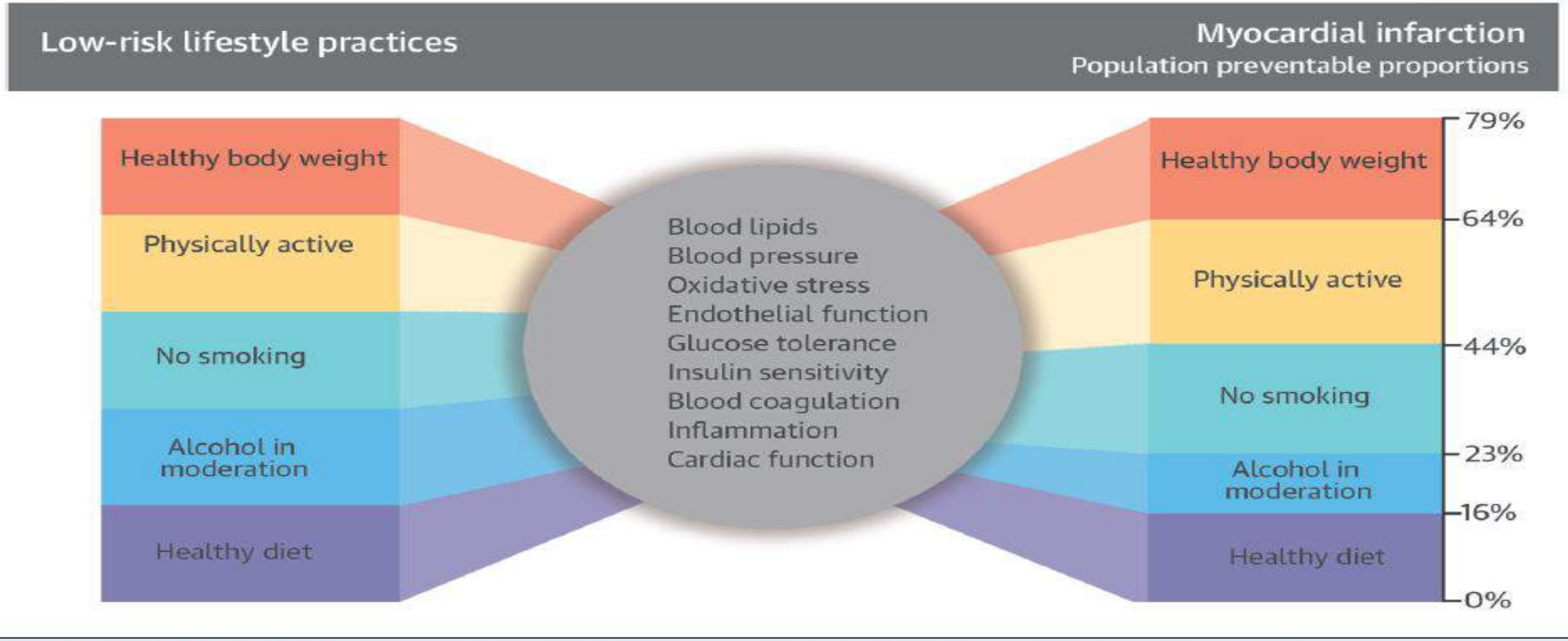
# Consultation “Lipides” aux HUG

- 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.

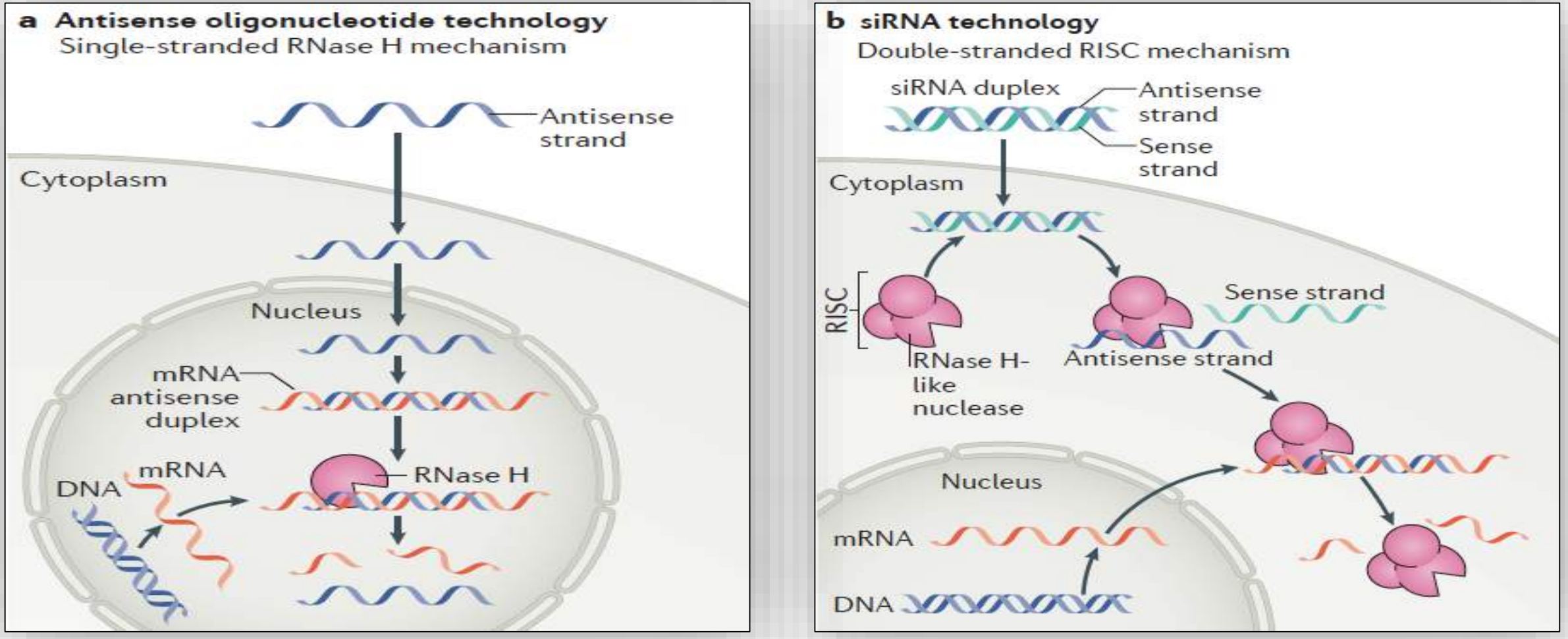
*JACC* 2014;64:93:12997

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*

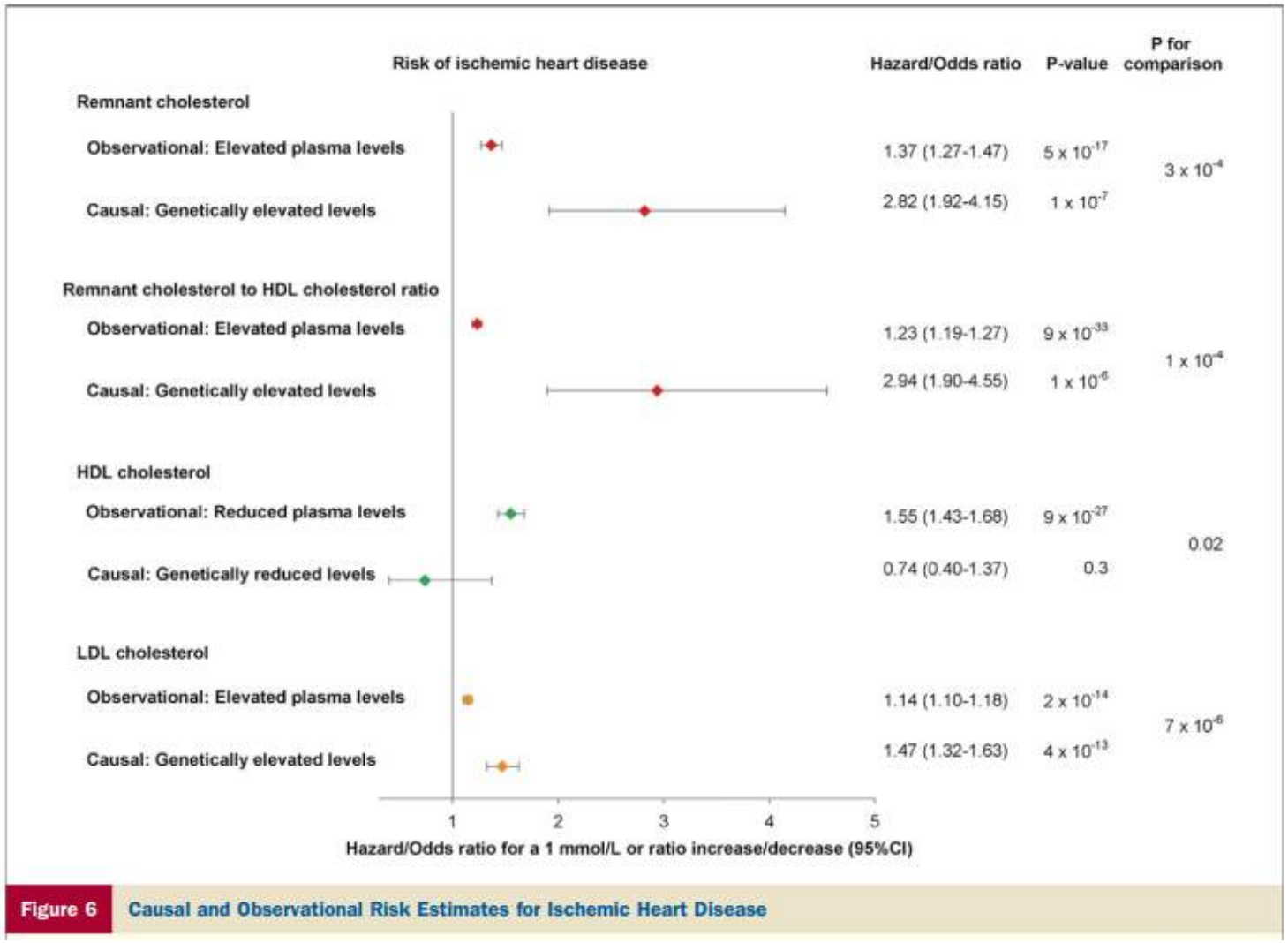



**Figure 6** Causal and Observational Risk Estimates for Ischemic Heart Disease



## Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease

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