DEUTSCHES HERZZENTRUM
DER CHARITÉ

Prof. Ulf
Landmesser

Efficacy and safety of siRNA and ASO therapeutics

31st January 2024
ESC Cardiovascular Roundtable

CHARITÉ

Efficacy and safety of
siRNA and ASO therapeutics

01 **Genetics of Cardiovascular Disease:**
Example of Advanced Understanding in Coronary Disease

02 **RNA-targeted Therapy – Efficacy:**
Example of Lowering Causal Lipoproteins for CVD

03 **RNA-targeted therapy – Safety:**
Example of Lowering Causal Lipoproteins for CVD

Genes mapped to coronary disease risk loci and pathophysiological pathways in atherosclerosis

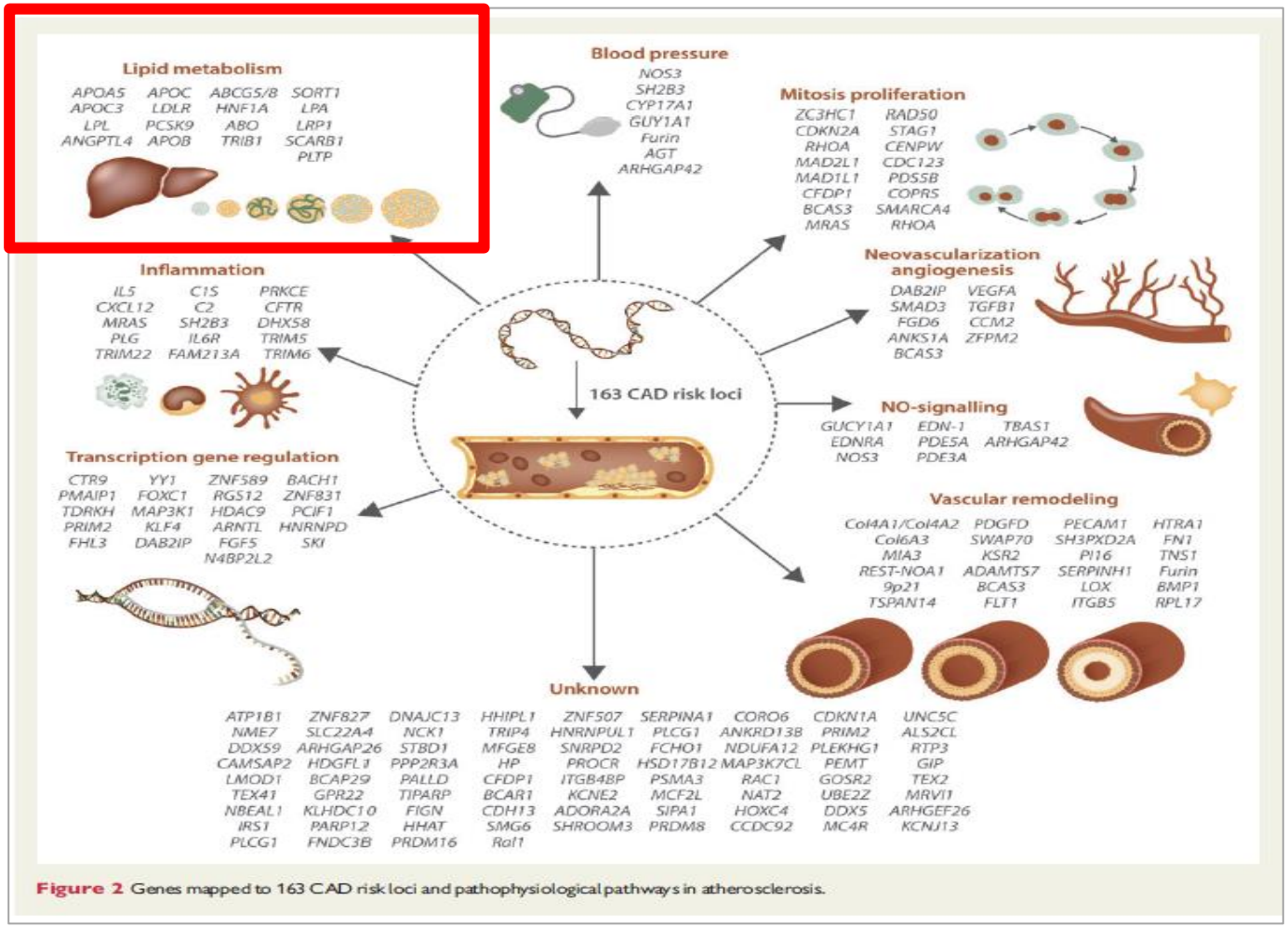


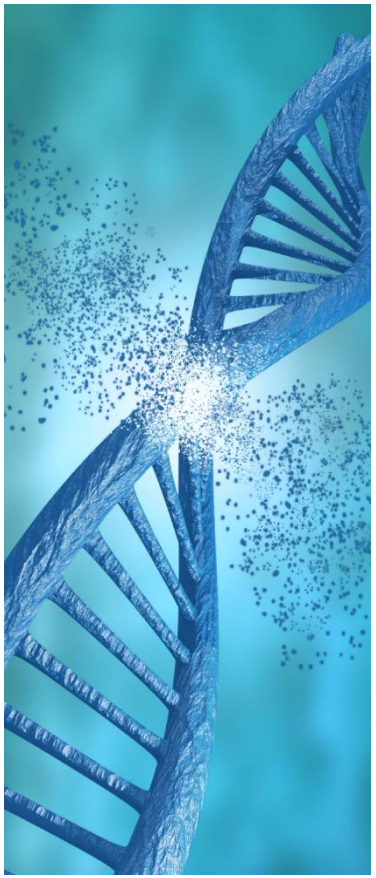
Figure 2 Genes mapped to 163 CAD risk loci and pathophysiological pathways in atherosclerosis.

Erdmann J et al. & Schunkert H. *Cardiovasc Res* 2018; 114(9):1241-1257
Aragam K et al.; *Nat Genet* 2022; 54(12):1803-1815 - CARDIoGRAMplusC4D Consortium
(currently > 240 genom-wide associations)

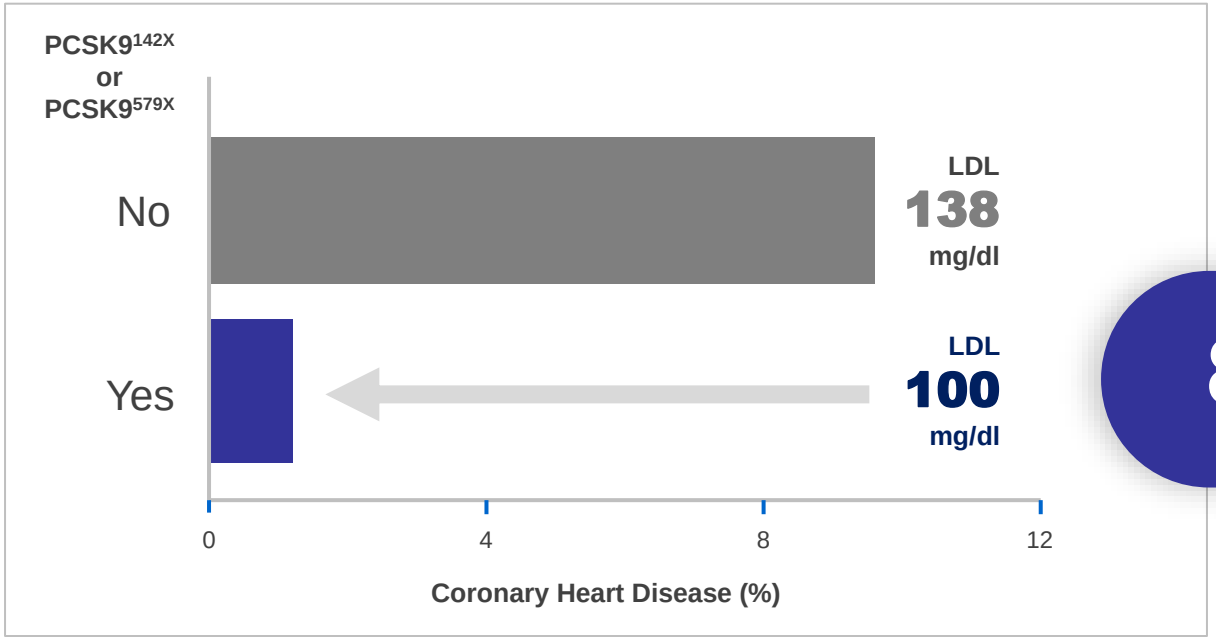
Observational, Genetic and Clinical Studies: Lipoproteins and Coronary Disease

	CORONARY DISEASE RISK		
		Genetic Studies	Clinical Studies
LDL cholesterol			
HMG-CO Reductase	↓	↓	↓
NPC1L1	↓	↓	↓
PCSK9	↓	↓	↓
Lipoprotein (a)	↑	↑	?
Triglyceride-Rich Lipoproteins:			
ApoCIII	↓	↓	?
ANGPTL3 /4	↓	↓	?
HDL-Cholesterol			
Endothelial Lipase	↑	↔	?
SR-B1	↑	↔↑	?

Landmesser U, Hazen S. **Eur Heart J** 2018; 39: 2179-2182



PCSK9 Sequence Variant and Coronary Disease



88% Reduced Risk of Coronary Disease

Cohen JC et al., **N Engl J Med** 2006; 354:1264-1272

Ferrence B,.., Landmesser U et al. **Eur Heart** 2017; 38: 2459-2472

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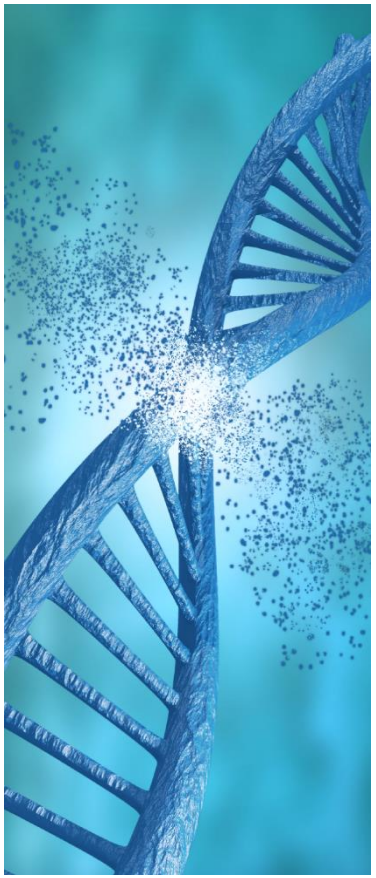
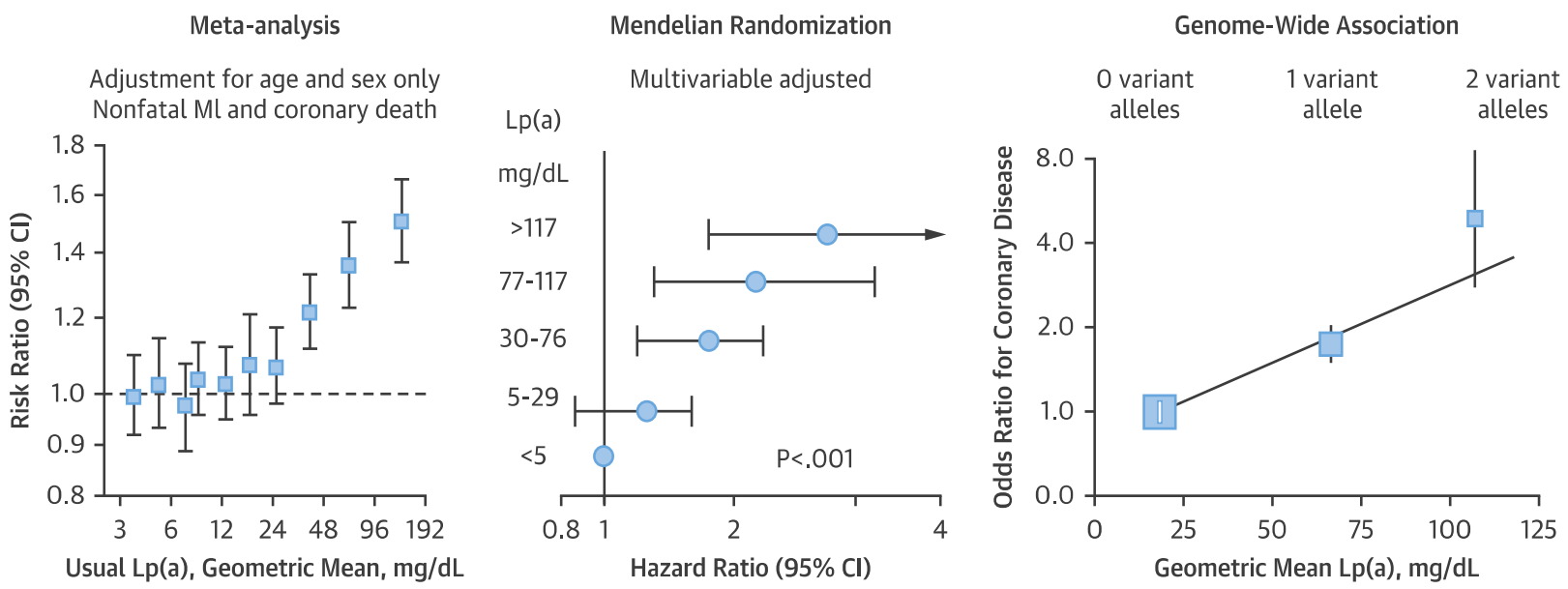


Landmesser U, Hazen S. **Eur Heart J** 2018; 39: 2179-2182

Lipoprotein (a) and Coronary Disease
(Non-fatal MI and Coronary Death)

FIGURE 4 Evidence Base for Lp(a) as an Independent, Causal, Genetic Risk Factor for CVD



Tsimikas S. J Am Coll Cardiol. 2017; 69(6):692-711

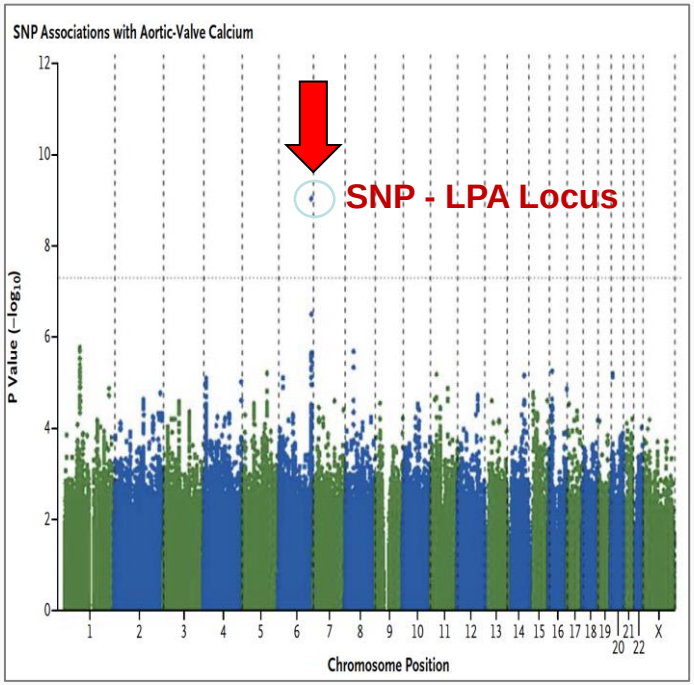
Genetic associations: Lipoprotein(a) and aortic valve calcification/stenosis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 7, 2013 VOL. 368 NO. 6

Genetic Associations with Valvular Calcification and Aortic Stenosis

George Thanassoulis, M.D., Catherine Y. Campbell, M.D., David S. Owens, M.D., J. Gustav Smith, M.D., Ph.D., Albert V. Smith, Ph.D., Gina M. Peloso, Ph.D., Kathleen F. Kerr, Ph.D., Sonali Pechlivanis, Ph.D., Matthew J. Budoff, M.D., Tamara B. Harris, M.D., Rajeev Malhotra, M.D., Kevin D. O'Brien, M.D., Pia R. Kamstrup, M.D., Ph.D., Børge G. Nordestgaard, M.D., D.M.Sc., Anne Tybjaerg-Hansen, M.D., D.M.Sc., Matthew A. Allison, M.D., M.P.H., Thor Aspelund, Ph.D., Michael H. Criqui, M.D., M.P.H., Susan R. Heckbert, M.D., Ph.D., Shih-Jen Hwang, Ph.D., Yongmei Liu, Ph.D., Marketa Sjogren, Ph.D., Jesper van der Pals, M.D., Ph.D., Hagen Kälsch, M.D., Thomas W. Mühleisen, Ph.D., Markus M. Nöthen, M.D., L. Adrienne Cupples, Ph.D., Muriel Caslake, Ph.D., Emanuele Di Angelantonio, M.D., Ph.D., John Danesh, F.R.C.P., Jerome I. Rotter, M.D., Sigurdur Sigurdsson, M.Sc., Quenna Wong, M.S., Raimund Erbel, M.D., Sekar Kathiresan, M.D., Olle Melander, M.D., Ph.D., Vilmundur Gudnason, M.D., Ph.D., Christopher J. O'Donnell, M.D., M.P.H., and Wendy S. Post, M.D., for the CHARGE Extracoronary Calcium Working Group



Conclusions: Genetic variation in the **LPA locus**, mediated by Lp(a) levels, is associated with aortic valve calcification across multiple ethnic groups and with **incident clinical aortic stenosis**.

Thanassoulis G et al., N Engl J Med 2013; 368(6):503-12

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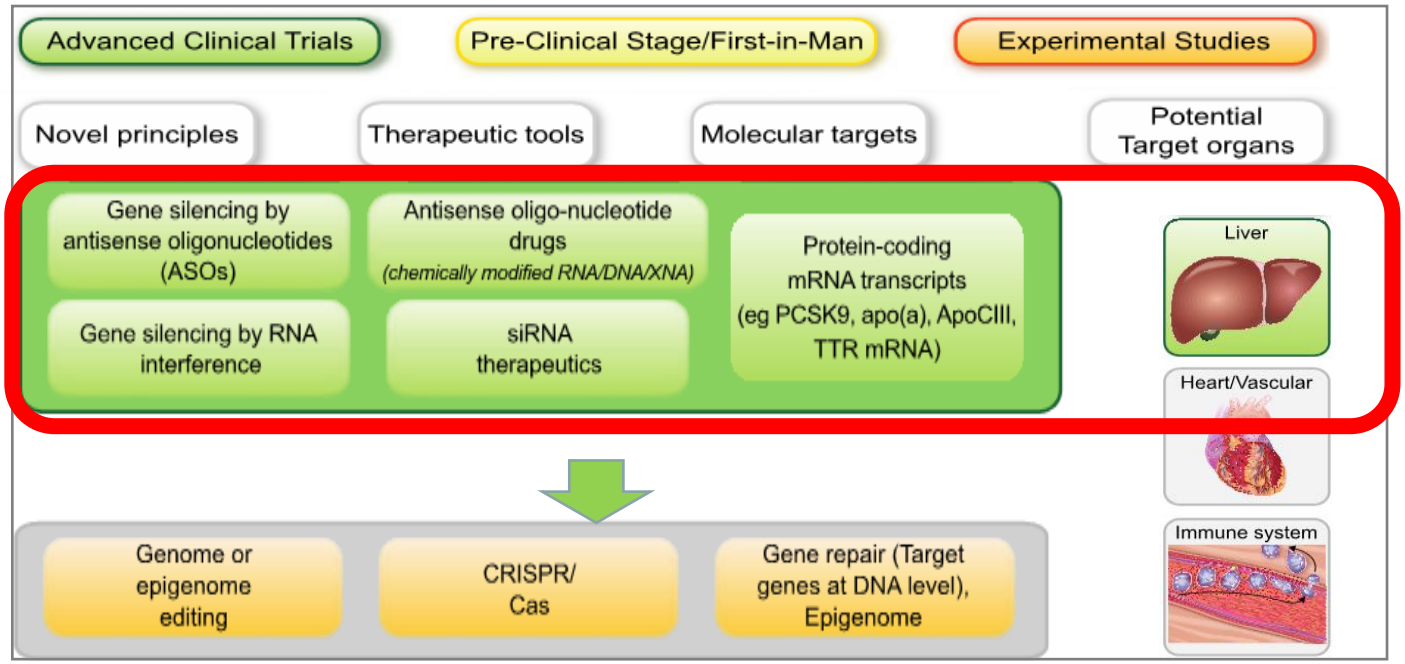
ESC European Society of Cardiology
European Heart Journal (2020) **00**, 1–23
doi:10.1093/eurheartj/ehaa229

CLINICAL REVIEW
Disease management

From traditional pharmacological towards nucleic acid-based therapies for cardiovascular diseases



Landmesser U et al & Lüscher T. *Eur Heart J* 2020; 41: 3884-3899

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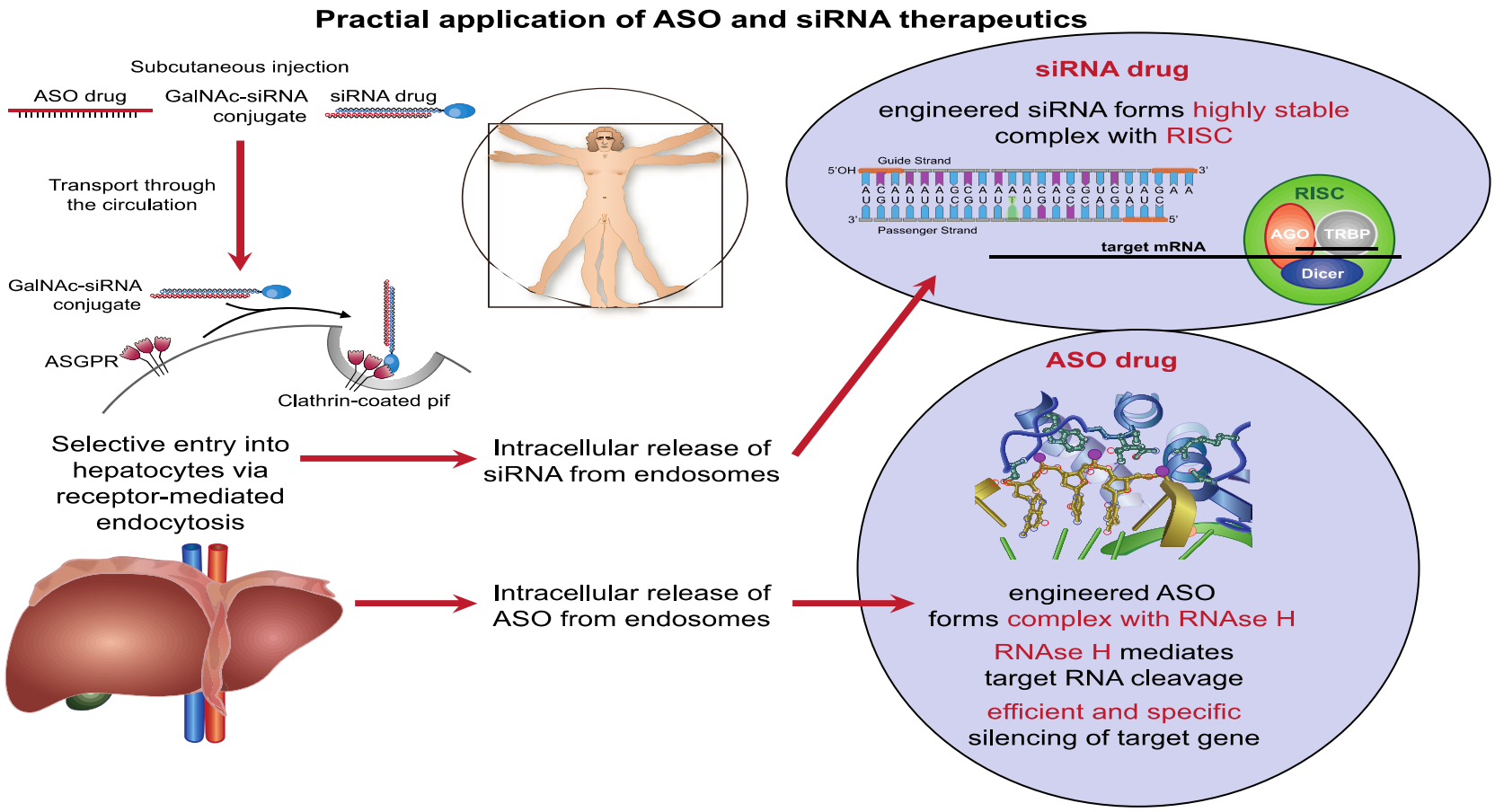


Landmesser U et al & Lüscher T. *Eur Heart J* 2020; 41: 3884-3899

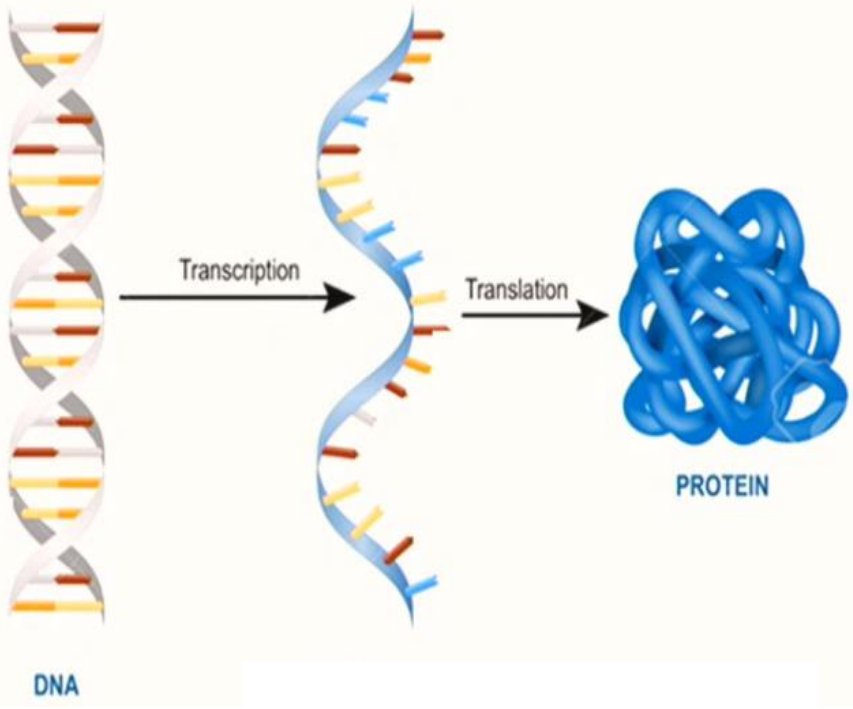
RNA-targeted therapies –
Targeting mRNA to prevent protein synthesis

Transcription

- Process by which genetic information encoded in DNA is copied to mRNA
- Occurs in the nucleus

Translation

- Process by which information encoded in mRNA is used to synthesize a protein at a ribosome
- Occurs in the cytoplasm

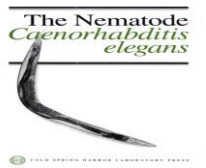


RNA interference

(small interference RNAs – siRNAs)

- Small interfering RNA (siRNA) therapies represent a new approach to harness a natural biologic pathway called RNA interference (RNAi)
- By means of RNAi, our bodies regulate the production of different proteins
- Researchers first discovered RNAi in 1998. The 2006 Nobel Prize for Physiology or Medicine, awarded to Craig Mello and Andrew Fire, recognized RNAi as a major scientific discovery
- Small interfering RNA (siRNA), sometimes known as short interfering RNA or silencing RNA, is a class of double-stranded RNA molecules, ~25 base pairs in length, operating within the RNA interference (RNAi) pathway
- It interferes with the expression of specific genes with complementary nucleotide sequences by degrading mRNA after transcription, preventing translation

Fire A, et al. & Mello CC.
Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans
Nature 1998; 391:806-11

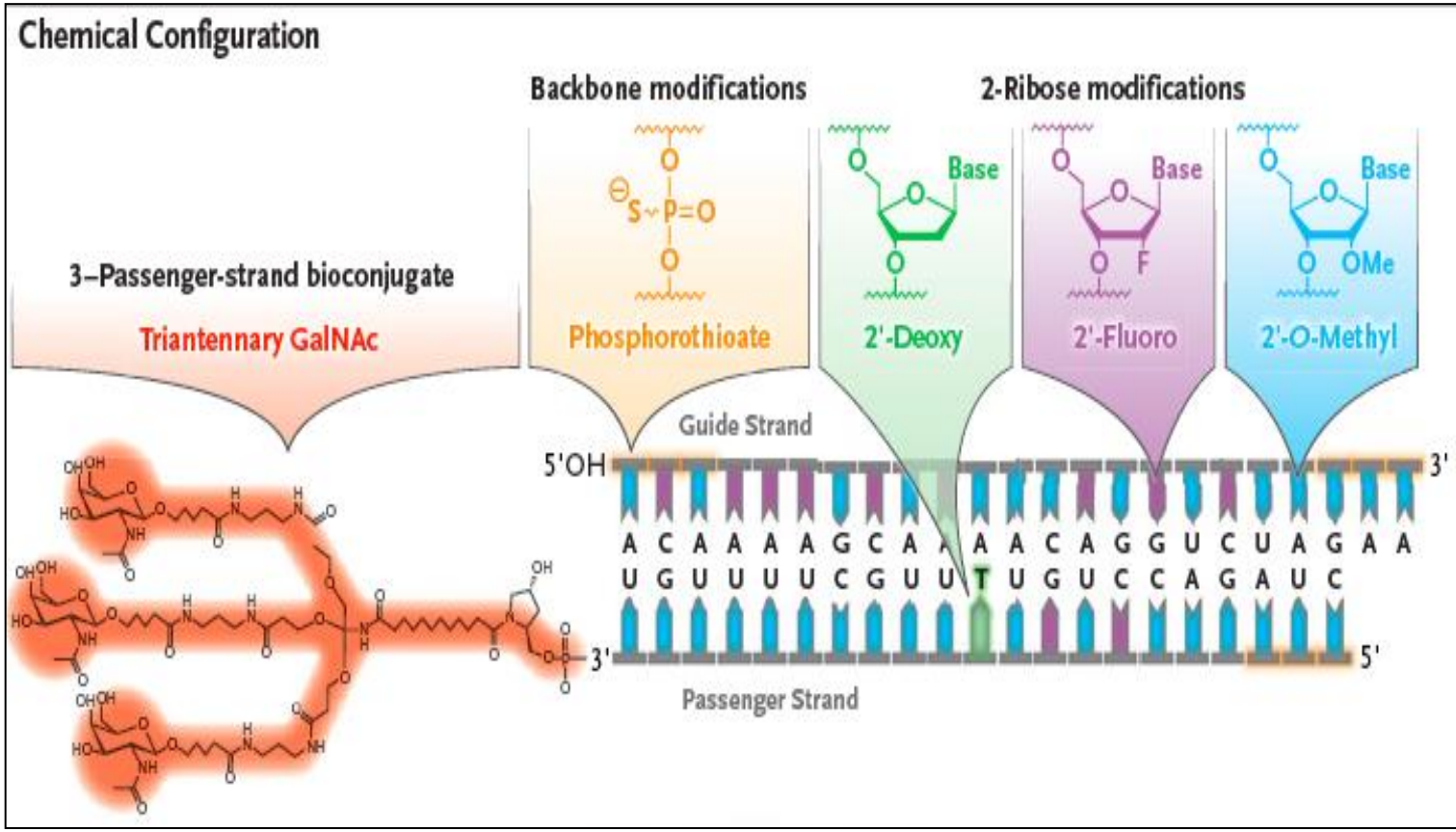


2006 Nobel Prize in Physiology or Medicine:
In their brilliant paper, Andrew Fire and Craig Mello demonstrated that **double-stranded RNA activates an enzymatic mechanism that leads to gene silencing**, with the genetic code in the RNA molecule determining which gene to silence.

Therapeutic siRNA – targeting PCSK9 (Inclisiran)

Structure and chemical modifications; Conjugated Targeting molecule

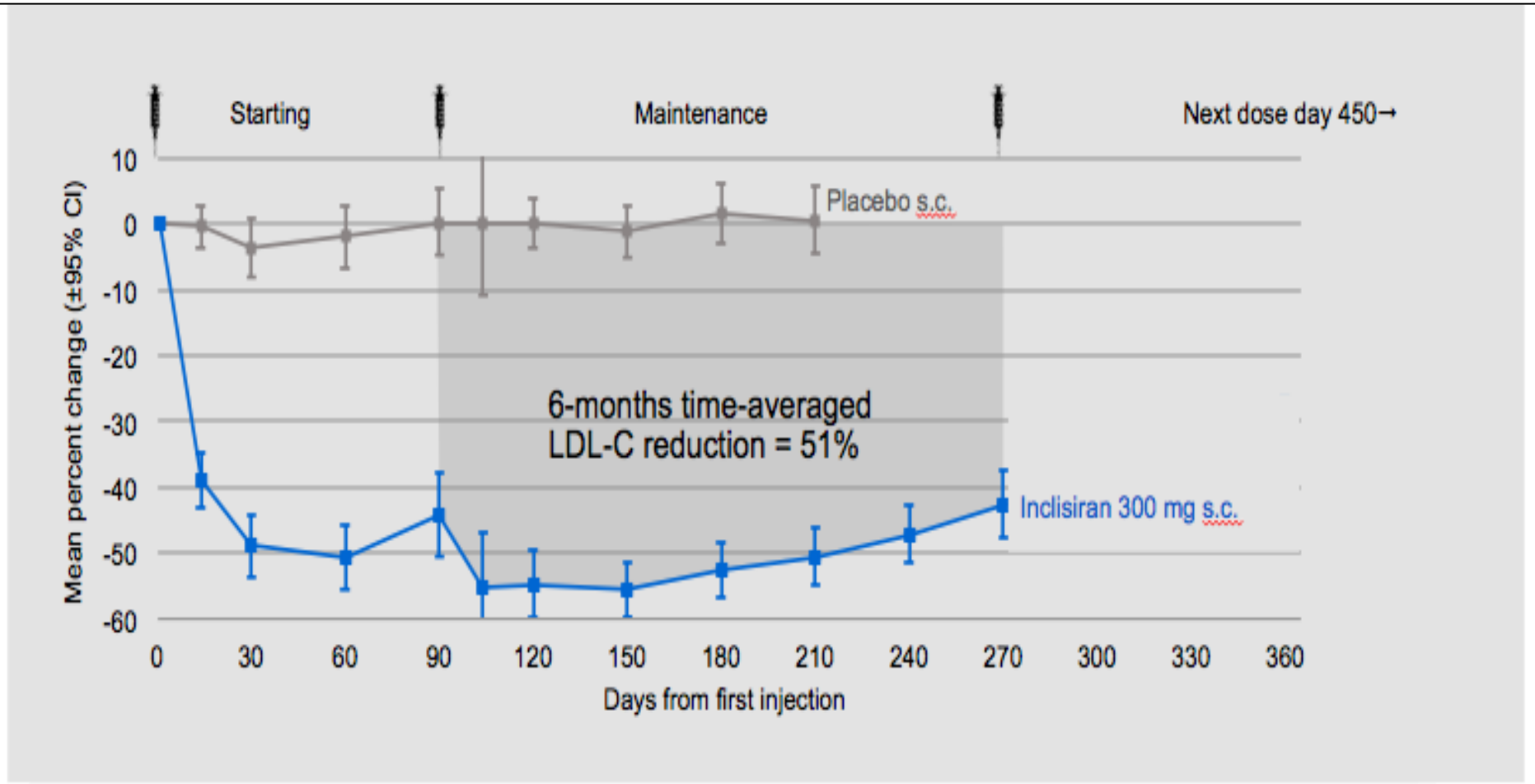
1. Nucleotide Modifications



2. GalNAc Conjugation – Targeting the Asialo-glycoprotein receptor (ASGPR)

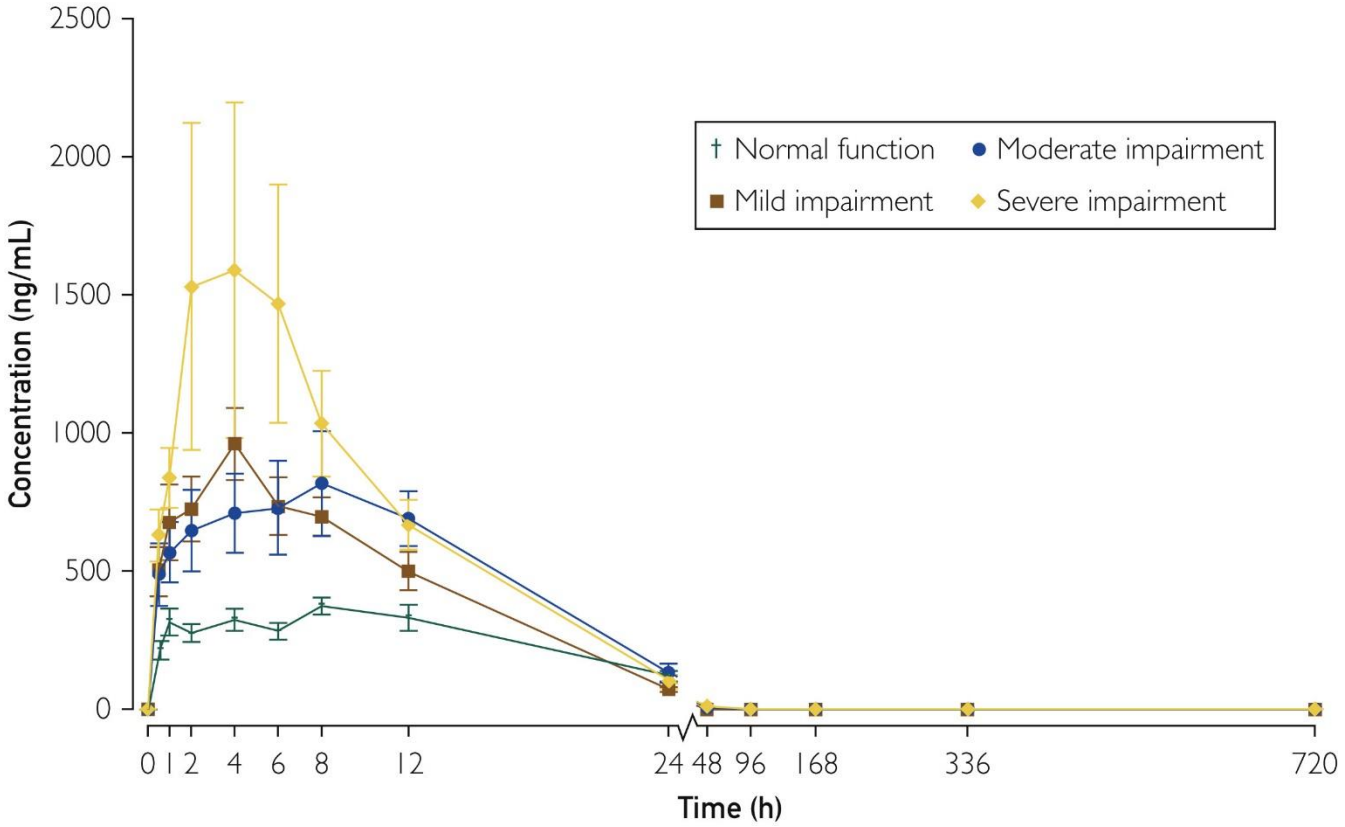
Khvorova A. *N Engl J Med* 2017

PCSK9 siRNA – ORION-1 Phase 2 Study:
Long-lasting effects of of 300 mg s.c. PCSK9 siRNA



Ray K*; Landmesser U* et al. *N Engl J Med* 2017;376:1430-1440

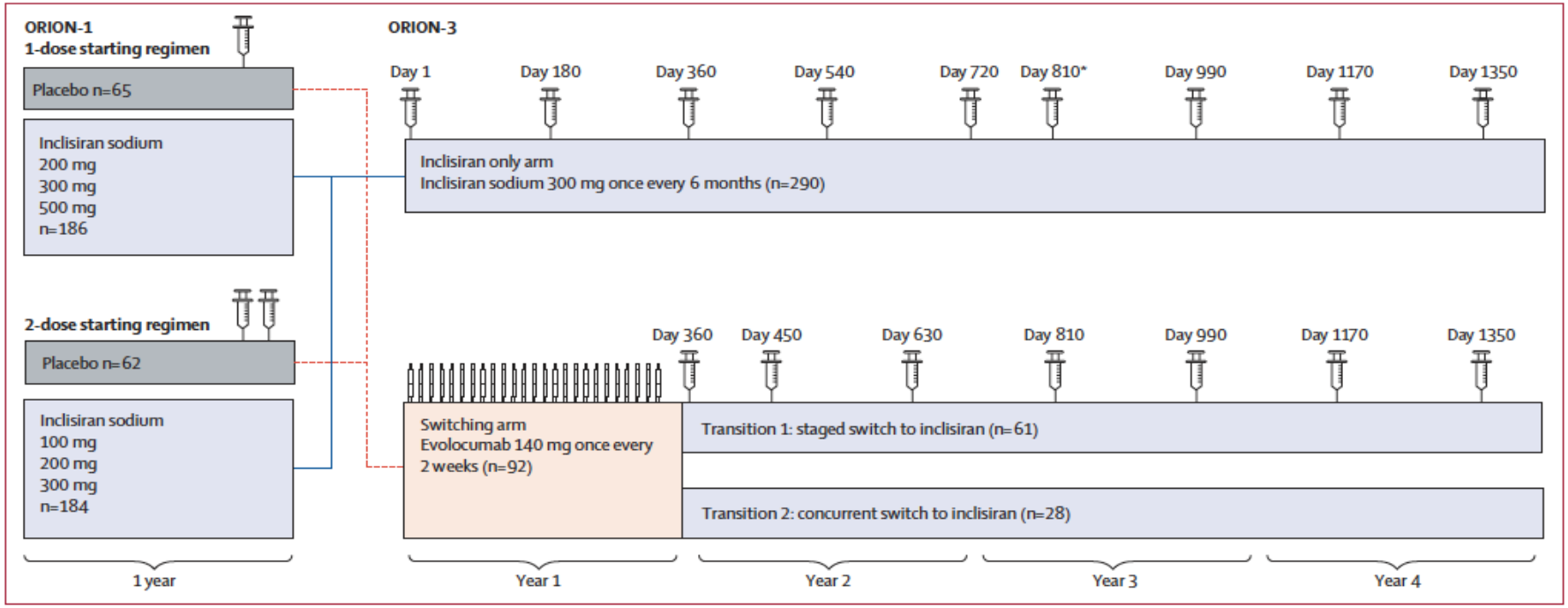
New Pharmacokinetics:
PCSK9 siRNA Plasma concentrations



Mayo Clin Proc 2020; 95: 77-89

Long-term efficacy and safety of inclisiran in patients with high cardiovascular risk and elevated LDL cholesterol (ORION-3): results from the 4-year open-label extension of the ORION-1 trial

Kausik K Ray, Roel P T Troquay, Frank L J Visseren, Lawrence A Leiter, R Scott Wright, Sheikh Vikarunnessa, Zsolt Talloczy, Xiao Zang, Pierre Maheux, Anastasia Lesogor, Ulf Landmesser



Lancet Diabetes Endocrinol. 2023; 11(2):109-119

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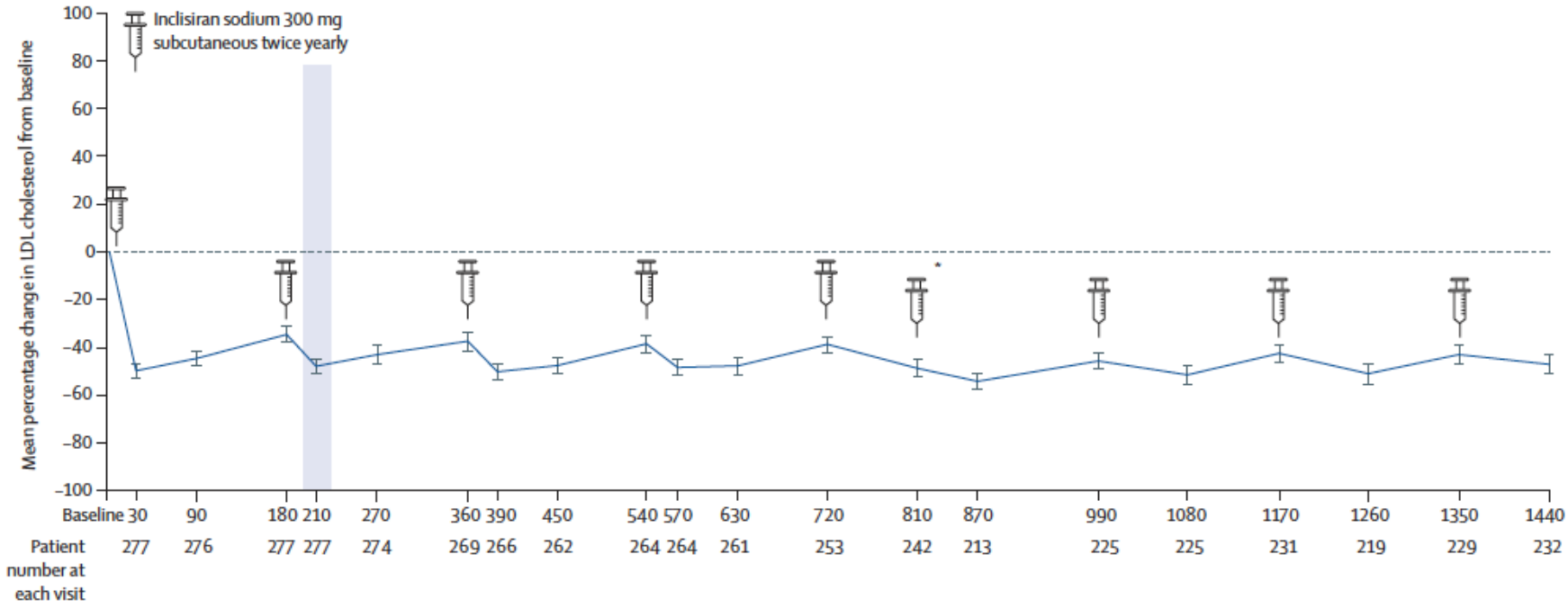

Lancet Diabetes Endocrinol. 2023; 11(2):109-119

Circulation

EDITORIAL

New Chapter in the PCSK9 Book: Oral Inhibition of PCSK9 Binding to the LDL Receptor With a Macrocyclic Peptide

Ulf Landmesser, MD; Umidakhon Makhmudova, MD

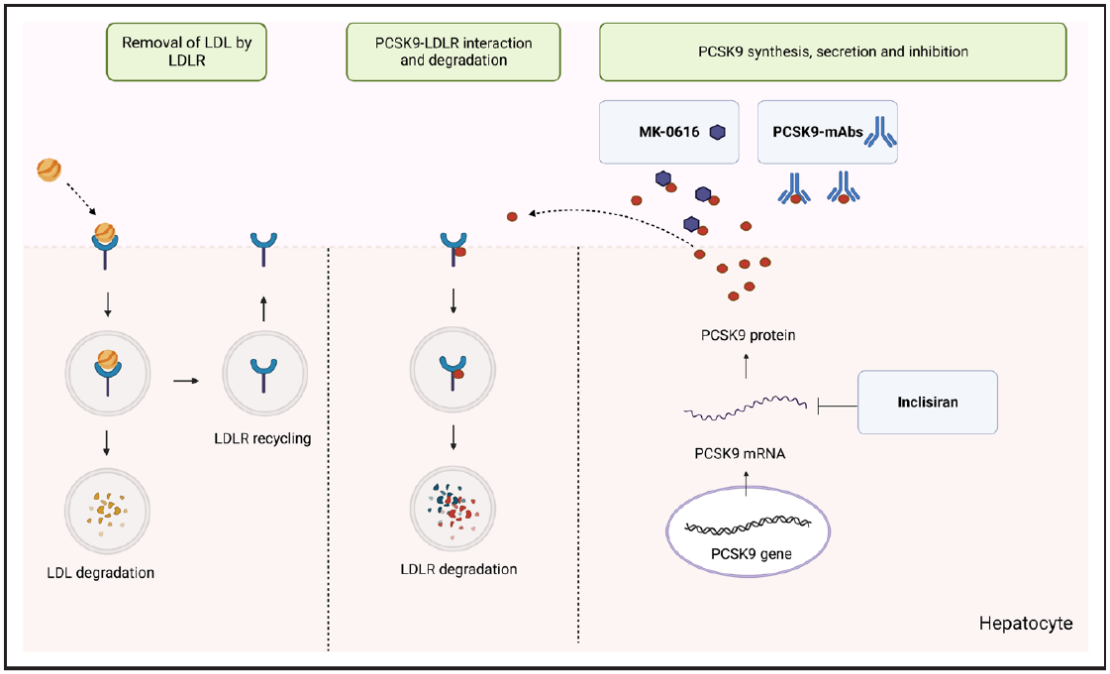

Figure. LDLR mediates the endocytosis and subsequent degradation of cholesterol-rich LDL.

Circulation 2023

Observational, Genetic and Clinical Studies: Atherogenic Lipoproteins and Coronary Disease

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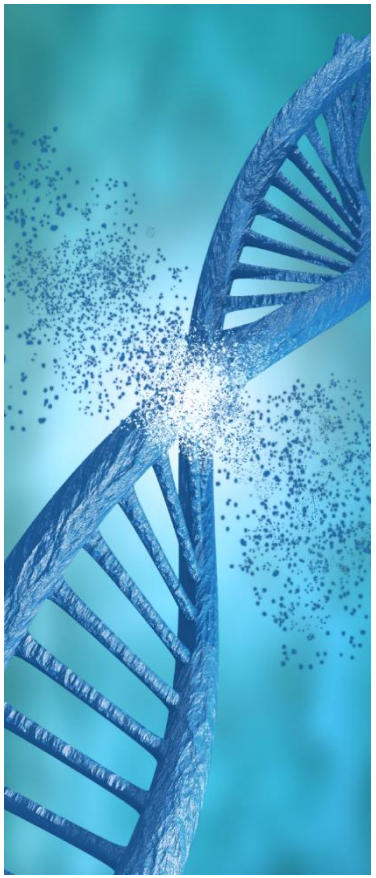
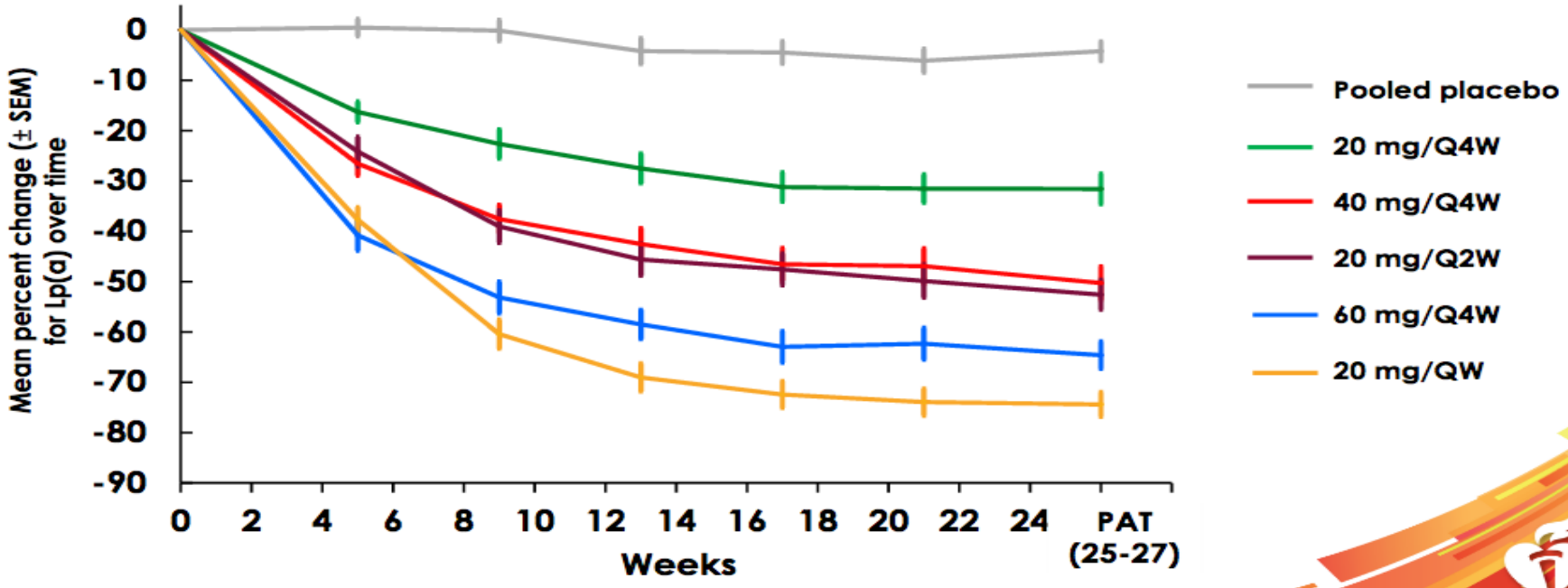
Landmesser U, Hazen S. **Eur Heart J** 2018; 39: 2179-2182



Lipoprotein (a) Antisense oligonucleotide therapy: Phase 2 Study

Primary endpoint: Mean percent change (SEM) in Lp(a) from baseline to week 25-27



PAT, primary analysis timepoint; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks; SEM, standard error of the mean.

Tsimikas S et al. *N Engl J Med*. 2020 Jan 16;382(3):244-255

The NEW ENGLAND JOURNAL of MEDICINE

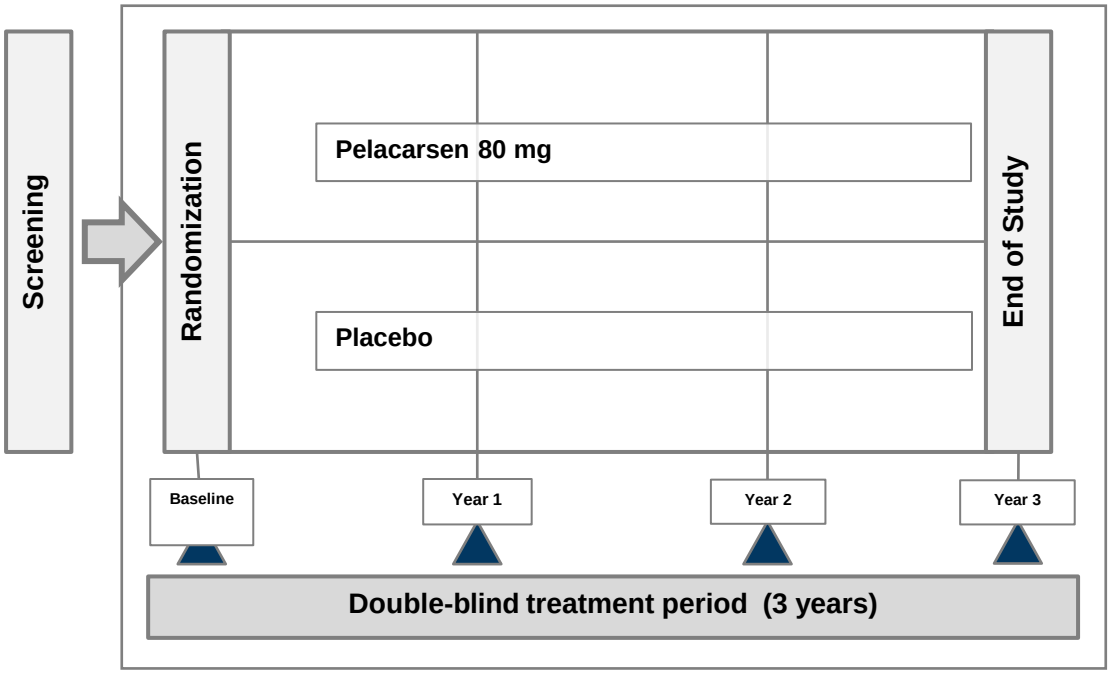
The Changing Landscape of Aortic-Valve Stenosis Management

Ulf Landmesser, M.D.

- **Aortic-valve stenosis has a prevalence of > 2.5 % in adults > 75 years**
- **Current managment is largely limited to a decision on timing and mode of aortic-valve replacement.**
  (Relevant periprocedural risk and a bioprosthetic-valve failure rate >3% at 5 years)
- **There is a major unmet clinical need for medical treatment of aortic-valve stenosis – a highly frequent healthcare problem**

N Engl J Med. 2023 Nov 23;389(21):2008-2009

Lp(a)FRONTIERS CAVS: Study design



Aims:

- To assess the impact of Lp(a) lowering with pelacarsen on CAVS progression

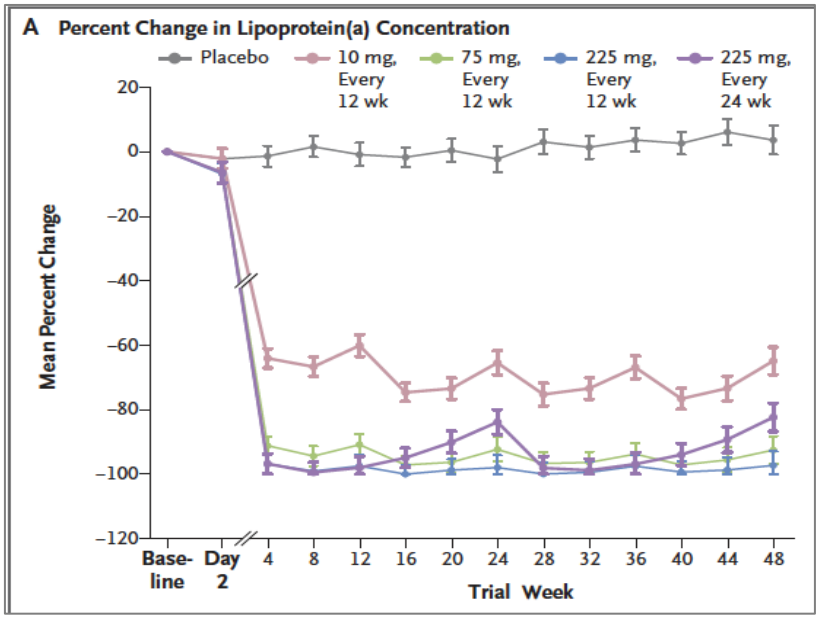
- To assess the impact of Lp(a) lowering with pelacarsen in atherosclerotic plaque features

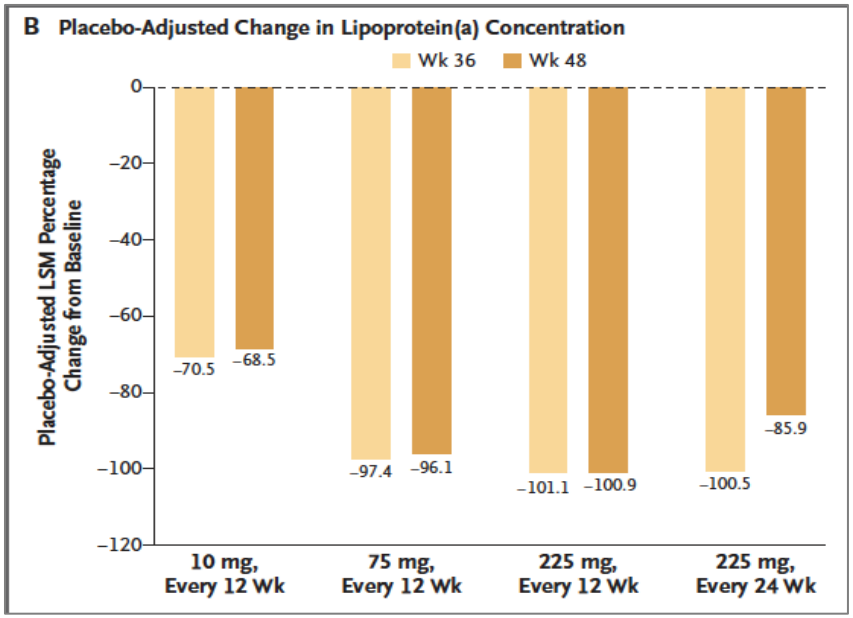
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D., Baris Gencer, M.D., M.P.H., J. Antonio G. López, M.D., Norman E. Lepor, M.D., Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D., Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S., Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D., Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H., for the OCEAN(a)-DOSE Trial Investigators*





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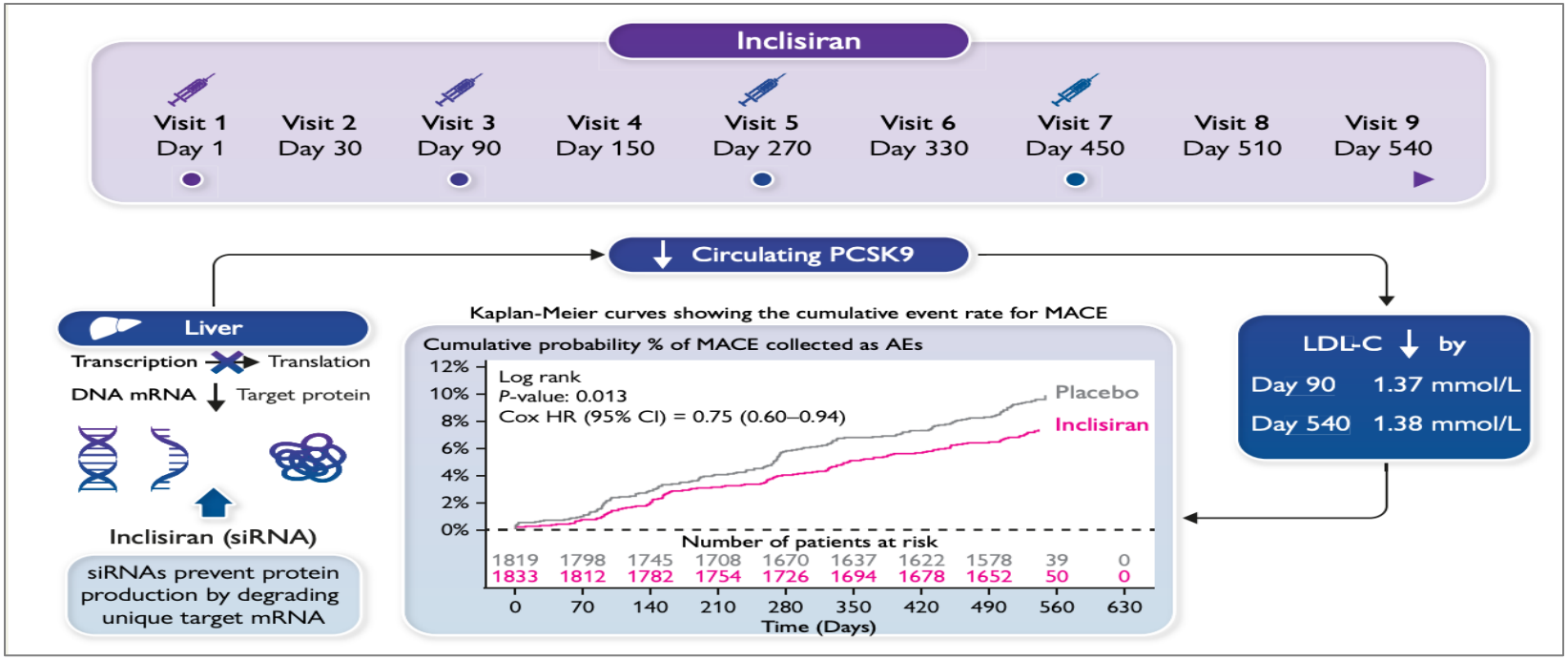
ESC European Society of Cardiology

European Heart Journal (2023) **44**, 129–138
https://doi.org/10.1093/eurheartj/ehac594

FASTTRACK CLINICAL RESEARCH
Epidemiology and prevention

Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

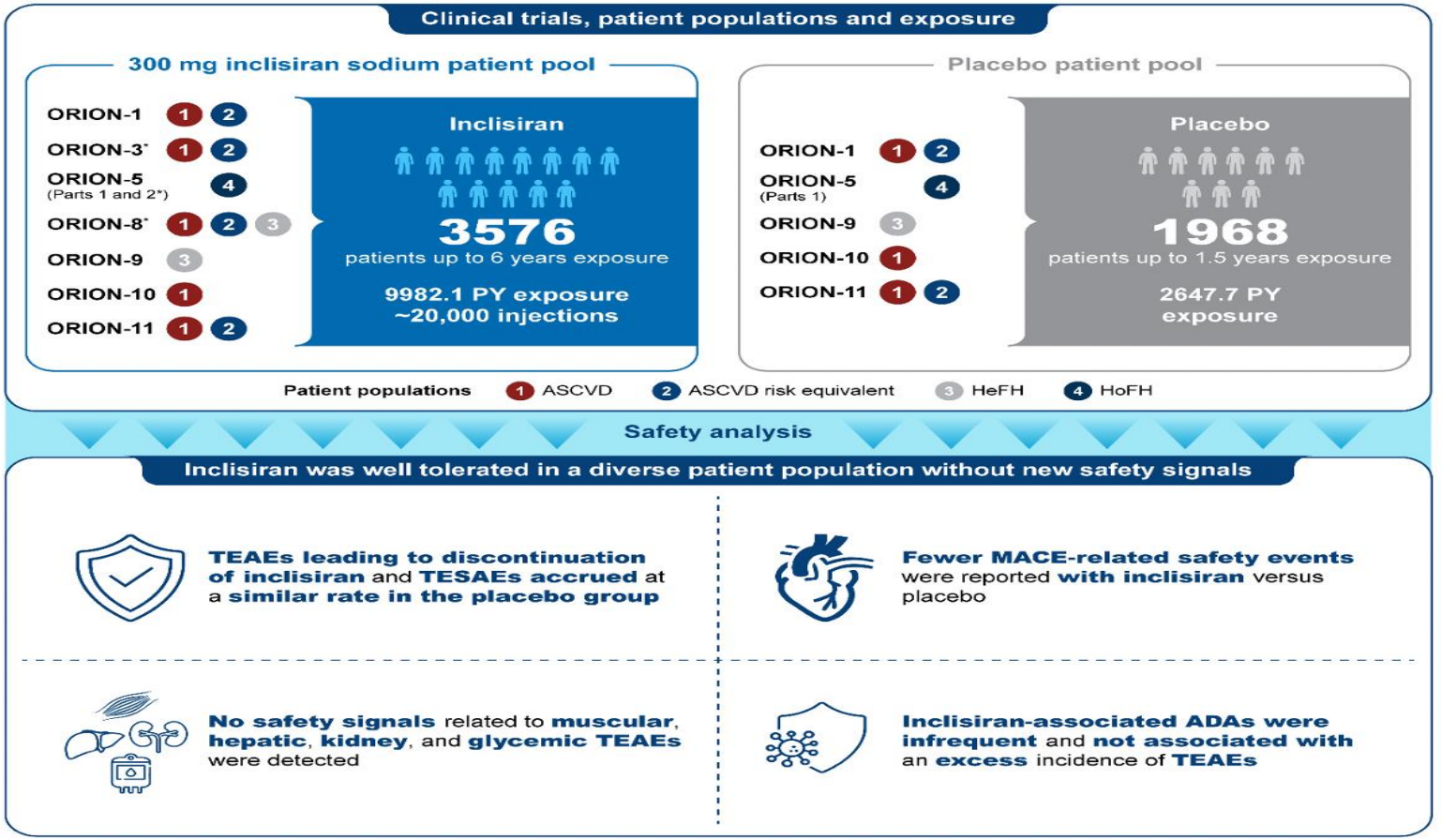
Kausik K. Ray [1]*, Frederick J. Raal[2], David G. Kallend[3,4†], Mark J. Jaros[5], Wolfgang Koenig [6,7], Lawrence A. Leiter[8], Ulf Landmesser [9],



Eur Heart J 2023; 44(2):129-138

ORION pooled analysis: Safety and tolerability of inclisiran in 7 clinical trials

No safety signals for muscular, hepatic, kidney, or glycemic TEAE



Wright RS, König W, Landmesser U et al.
J Am Coll Cardiol 2023 Dec 12;82(24):2251-2261

Clinical Outcome Trials (selected) with targeted (GalNaC-conjugated) siRNAs/ASOs for Causal Lipoproteins for CVD

siRNA PCSK9

- ORION-4
- VICTORION-2-PREVENT

ASO Lp(a)

- HORIZON

siRNA Lp(a)

- OCEAN

ASO ApoCIII

- CORE Program

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–2
doi:10.1093/eurheartj/ehab532

CARDIOPULSE

Braunwald's Corner

How to live to 100 before developing clinical coronary artery disease: a suggestion

Eugene Braunwald [1,2*]

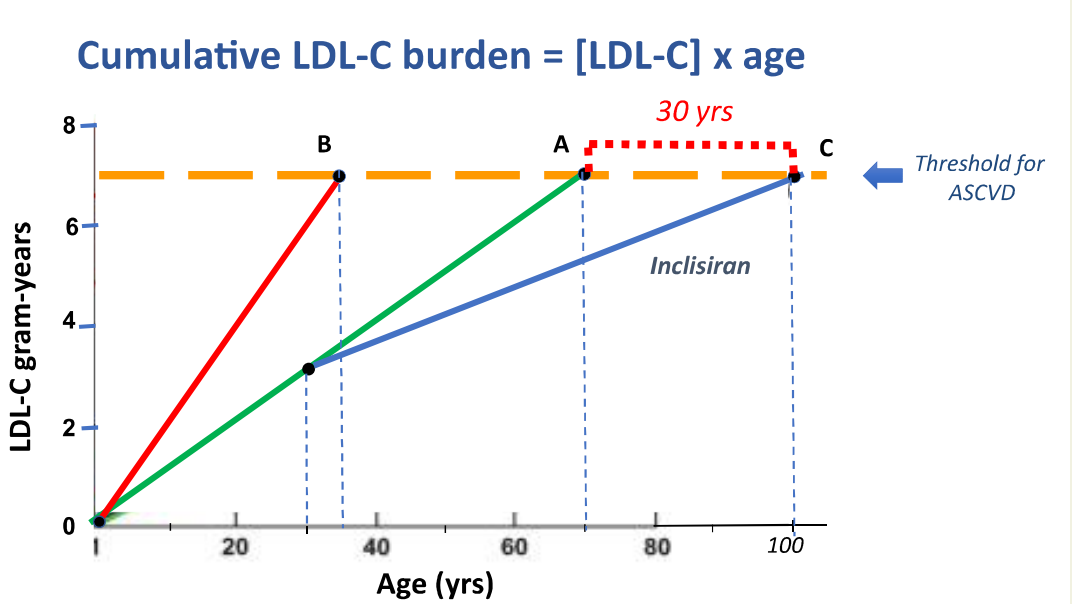


Figure 1 Modified from Horton *et al.*[12]

- ASCVD threshold of 7 LDL-C gram-years
- Red line FH LDL-C 200 mg/dl
- Green line LDL-C 100 mg/dl
- Blue line – LDL-C 100 mg/dl, but PCSK9 siRNA from age 30 years

ESC European Society of Cardiology
European Heart Journal (2020) **00**, 1–23
doi:10.1093/eurheartj/ehaa229

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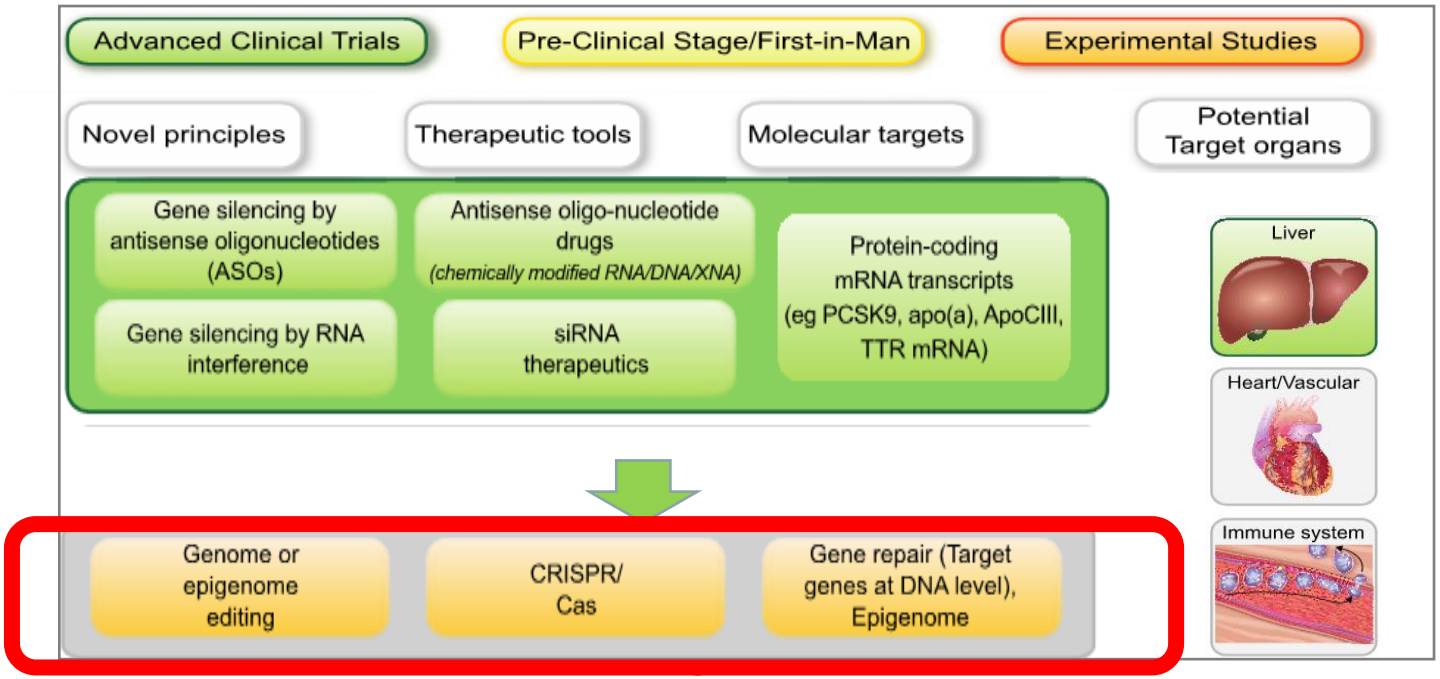

Landmesser U et al & Lüscher T. *Eur Heart J* 2020; 41: 3884-3899

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Thank you !

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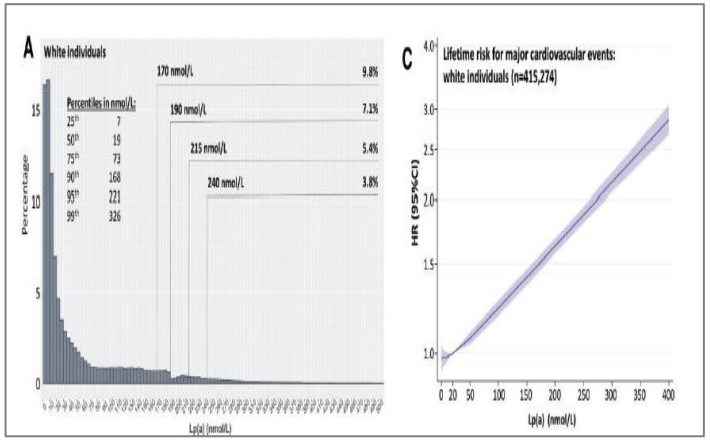
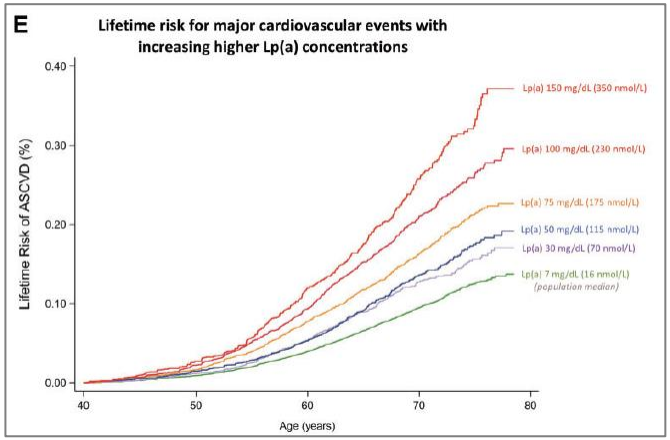
European Heart Journal (2022) **0**, 1–22
https://doi.org/10.1093/eurheartj/ehac361

SPECIAL ARTICLE
Miscellaneous

Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis:





Kronenberg F et al.; Eur Heart J. 2022 Aug 29 (Online ahead of print)

DHZC