Lowering Cholesterol.

Saving Lives.

Tackling Cholesterol Together

Novel therapies- now and future

Welcome to the seventh in a series of webinars as part of the national education programme Tackling Cholesterol Together.

Delivered in partnership by The NHS Accelerated Access Collaborative (AAC), The AHSN Network and the cholesterol charity, HEART UK

The webinar will start at 11am

Dec 2021

All programme content, recordings and next webinar bookings will be housed in the HEART UK pages. Visit the site for the **new** e-Learning module on Statin Intolerance. https://www.heartuk.org.uk/tackling-cholesterol-together/home


Tackling Cholesterol Together
TheAHSNNetwork
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THE CHOLESTEROL CHARITY
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CHOLESTEROL
This campaign is being funded by Novartis Pharmaceuticals UK Ltd. as part of a collaborative working agreement for lipid management, with NHS England & Improvement (NHSE&I) and Accelerated Access Collaborative (AAC). Novartis, NHSEI& and AAC contribute resources in the form of skills, expertise, project management and administrative activity. Novartis has approved the associated materials in line with the ABPI Code.
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Housekeeping

- **This meeting will be recorded** and will be made available in the HEART UK Tackling Cholesterol Together pages
- **There will be time** to stop and ask questions at the end of the webinar
- **Feel free to ask questions** or upvote questions in the chat function when it becomes available
- **Any questions that we are not able to cover in the Q&A** sections today will be addressed following the event
- **Any questions you provided** during registration will be covered during the session

Agenda

	Topic	Presenter
01	**Welcome**	Sue Critchley
02	**NICE recommendations**	Dr Ameet Bakhai
03	**Novel Therapies- setting the scene**	Dr Yassir Javaid
04	**Inclisiran- What is it, how does it work and in whom do I use it ?**	Professor Kausik K Ray
05	**Q&A. Close and next steps**	Sue Critchley

Objectives of today's webinar

01

Review briefly the most recent NICE recommendations (CG181, TA733, TA694, NG197). **Review** the burden of CVD in the UK.

02

Consider progress made in tackling CVD mortality and the remaining challenge. **Review** evidence that that LDL-C has both a causal and a cumulative effect on the risk of cardiovascular disease.

03

Understand the clinical disease stages.

Consider if we have reached the limits of LDL-C lowering, why we should target PCSK9 and if we have reached the limits of cardiovascular outcomes.

04

Appreciate the therapeutic approaches to reducing LDL-C via the LDL receptor small molecules, Mabs and siRNA, and **see** the efficacy and safety data from ORION trials.

02

Recent NICE recommendations

Dr Ameet Bakhai
Consultant Cardiologist and Research Director. Royal Free London NHS Foundation Trust

Disclosures

- **Consultancy / Educational Honoraria:**
  Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, BMS, Closer Still Media, Daiichi Sankyo, Janssen, Lilly, Medtronic, McKinsey, MSD, Napp, NICE, Novartis, Novo Nordisk, Oxford Outcomes, Pfizer, Remedica, Sanofi Aventis, Wave. Amore Health Ltd (Director & Founder)

NICE strategy 2021 to 2026

NICE's core purpose

Improving health and wellbeing by putting science and evidence at the heart of health and care decision making

Pillar 1

Rapid, robust and responsive technology evaluation

Pillar 2

Dynamic, living guideline recommendations

Pillar 3

Effective guidance uptake to maximise our impact

Pillar 4

Leadership in data, research and science

Recommendations and Tools for Effectively Screening Patients for High-Risk and Very-High-Risk CVD, and FH

NICE recommendations[1]

- Use a systematic strategy to screen patients
- Prioritise people on the basis of an estimate of their CVD risk before a full formal risk assessment
- Use CVD risk factors recorded in primary care electronic medical records to estimate risk
- Prioritise people for a full formal risk assessment if their estimated 10-year CVD risk is ≥10%
- People >40 years old should have their CVD risk reviewed on an ongoing basis

QRISK®2 online tool

- Tool to assess CVD risk for the primary prevention of CVD in people aged ≤84 years[1,2]
- **NOT** to be used in patients with:[2]
  - Suspected/confirmed FH
  - Type 1 diabetes
  - Pre-existing CVD
  - eGFR <60 mL/min/1.73 m^2 and/or albuminuria
- Available at:[3] https://qrisk.org/2017/

Primary Care FH Identification and Lipid Optimisation tools[4]

- Comprehensive search tools to select and risk stratify patients
- Integrate with EMIS and SystmOne
- Allow GP practices to prioritise patients for FH, primary and secondary prevention screening
- Example tools: CDRC Precision; PRIMIS FAMCAT; UCLP Proactive Care Frameworks

Inclisiran is an LDL-C lowering therapy that, with two maintenance doses a year (following an initial and a second dose at 3 months), delivered effective and sustained LDL-C reduction when used in combination with a maximally tolerated statin in patients with ASCVD (or risk equivalents)[1].

License: Leqvio (inclisiran) is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Efficacy*: inclisiran reduced LDL-C by 50% relative to placebo at Month 17, as compared with baseline, in patients with ASCVD (or risk equivalents) on a maximally tolerated statin in ORION-11 (95% CI: −53.1 to −46.6; P<0.0001)[1]

Posology: the recommended dose is 284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months[1]

Tolerability§: generally well tolerated, with the only adverse reactions associated with inclisiran being adverse reactions at the injection site (8.2%)[1]

NICE TA 733 recommends inclisiran as a treatment option for people with primary hypercholesterolaemia or mixed dyslipidaemia who have already had a cardiovascular event such as a heart attack or stroke.[2]

*Similar results were achieved in patients with ASCVD treated in ORION-10: at Month 17, inclisiran delivered placebo-corrected LDL-C reductions of 52%, as compared with baseline (95% CI: −55.7 to −48.8; P<0.0001).
ORION-10 (N=1,561) and ORION-11 (N=1,617) were multicentre, double-blind, randomised, placebo-controlled 18-month clinical trials evaluating adult patients with ASCVD, and with ASCVD or risk equivalents, respectively. (Optional: Patients were randomised (1:1) to receive a subcutaneous injection of inclisiran (284 mg) or matching placebo on the first day, at Month 3 and then every 6 months over a period of 18 months.)
ASCVD risk equivalents included type 2 diabetes, FH, or a 10-year risk of a cardiovascular event of ≥20% as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent.
§ In the pivotal trials, adverse reactions at the injection site occurred in 8.2% and 1.8% of inclisiran and placebo patients, respectively. All of these adverse reactions were mild or moderate and none were severe or persistent.

References: 1. . Leqvio Summary of Product Characteristics.. Available at: https://www.medicines.org.uk 2. National Institute for Health and Care Excellence. Technology appraisal guidance [TA733]Published: 06 October 2021 Available at: https://www.nice.org.uk/guidance/ta733

Why a PHM approach to implementing inclisiran?

The challenge: Despite significant efforts and initiatives by the health care system, the number of people dying prematurely from cardiovascular disease (CVD) is on the rise for the first time in 50 years[1]. There is clear evidence that cholesterol, and specifically low-density lipoprotein cholesterol (LDL-C) is a well-established modifiable risk factor in the prevention of CVD[2] . It is also well documented that sustained lowering of LDL-C can reduce the risk of cardiovascular events[3,4].

Introducing inclisiran: will form part of the lipid management pathway, providing an additional option for clinicians and patients in the management of cholesterol.

A Population health management approach aims to improve the health and wellbeing of an entire population while reducing health inequalities[5]. This approach will build on the momentum already generated by AHSNs and clinicians in the optimisation of lipid management.

To achieve the scale and volumes required to positively impact a nation's CV health, support the NHS Long term Plan ambitions and address challenges within the pathway, it is proposed that inclisiran initiation and management is carried out within the primary care setting by the primary care workforce where this patient population is managed and cared for[6].

Primary care implementation is essential to achieving a large-scale change in lipid management for patients with ASCVD

- Identification of patients with suboptimal cholesterol management
- Clinician and patient engagement on CVD risk management
- Improve and support patient adherence to treatment regime and lifestyle changes
- Provide ongoing opportunity for shared decision-making and support for patients
- Limit impact of inequity of access to health services
- Maximise impact of inclisiran within the lipid pathway to improve CVD risk management

References: [1] Heart UK. https://www.heartuk.org.uk/downloads/health-professionals/heart-uk-cvd-prevention-policy-paper---july-2019.pdf Accessed: January 2021. [2] Laight D. Prescriber 2018;29(8):13-18 https://doi.org/10.1002/psb.1694 [3] Ference BA et al. Eur Heart J 2017;38(32):2459-2472 . [4] Ference BA et al. J Am Coll Cardiol 2018;72(10):1141-1156. [5]. NHS England. Available at: https://imperialcollegehealthpartners.com/wpcontent/uploads/2018/07/Population-Health-Management-Flatpack-Version-1.0-Final-Sent.pdf. Accessed: January 2021. [6] Gov.uk. https://www.gov.uk/government/news/new-heart-disease-drug-to-be-made-available-for-nhs-patients [Accessed: March 2021].

NICE guidelines TA 694

Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

- Statins are contraindicated or not tolerated
- Ezetimibe alone does not control low-density lipoprotein cholesterol well enough and
- The company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement
- NICE was not able to evaluate the use of Bempedoic acid plus ezetimibe with low intensity statins when higher intensity statins are not tolerated

Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination.

NICE guidelines (NG197)

Shared decision making

- Shared decision making is a joint process in which a healthcare professional works together with a person to reach a decision about care.
- It involves choosing tests and treatments based both on evidence and on the person's individual preferences, beliefs and values.
- It makes sure the person understands the risks, benefits and possible consequences of different options through discussion and information sharing.

Benefits

- It allows people to discuss and share information. This makes sure people have a good understanding of the benefits, harms and possible outcomes of different options.
- It empowers people to make decisions about the treatment and care that is right for them at that time. This includes choosing to continue with their current treatment or choosing no treatment at all.
- It allows people the opportunity to choose to what degree they want to engage in decision making. Some people prefer not to take an active role in making decisions with their healthcare professionals.

Source: NICE guidelines (NG197) Shared Decision Making

03

Novel Therapies- setting the scene

Dr Yassir Javaid MA (Cantab) FRCGP FRCP PGDip Cardiology

G.P. Cardiovascular Lead Northamptonshire CCG 2013 - present

Primary Care CVD lead East Midlands Clinical Network (2013-2020)

Member of the editorial board for the British Journal of Cardiology.

Dr Javaid qualified from Cambridge University and completed his GP VTS training in Northampton. He has an interest in cardiology and echocardiography and was a clinical lead in the Northamptonshire Community Cardiology service, which had a focus on patients with heart failure and valve disease. He was named Pulse “GP of the Year” in 2015 for his work in reducing stroke emergency admissions in the East Midlands. He is also a member of the British Society of Echocardiography.

Disclosures

- **Honoraria received from:**
  Abbott, Amgen, Astra Zeneca, Bayer, BMS, Boehringer, Daiichi Sankyo, Edwards, iryhthm, Lilly, Medtronic, MSD, Napp, NovoNordisk, Novartis, Pfizer, Sanofi and Servier for various activities including attending and participating in educational events and advisory boards

The Burden of Cardiovascular Disease

CVD is responsible for 25% of all deaths in the UK

One death every 3 minutes in the UK

Costs the NHS in England around £7.4 billion per year

NHS – National Health Service

References: 1. BHF. https://www.bhf.org.uk/what-we-do/our-research/heart-statistics [Accessed: September 2021]. **2.** Gov.uk. https://publichealthmatters.blog.gov.uk/2019/02/14/health-matters-preventing-cardiovascular-disease/ [Accessed: April 2021].

Conclusion

Public Health England

Health Matters

10 year cardiovascular disease ambitions for England

Atrial fibrillation (AF)

85%

of the expected number of **people with AF are detected by 2029**

90%

of patients with AF who are already known to be at high risk of a stroke **to be adequately anticoagulated by 2029**

High blood pressure

80%

of the expected number of **people with high blood pressure are diagnosed by 2029**

80%

of the total number of people already diagnosed with high blood pressure are **treated to target as per NICE guidelines by 2029**

High cholesterol

75%

of people **aged 40 to 74 have received a formal validated CVD risk assessment** and **cholesterol reading** recorded on a primary care data system in the last five years by 2029

45%

of people **aged 40 to 74 identified as having a 20% or greater 10-year risk** of developing CVD in primary care are treated with statins by 2029

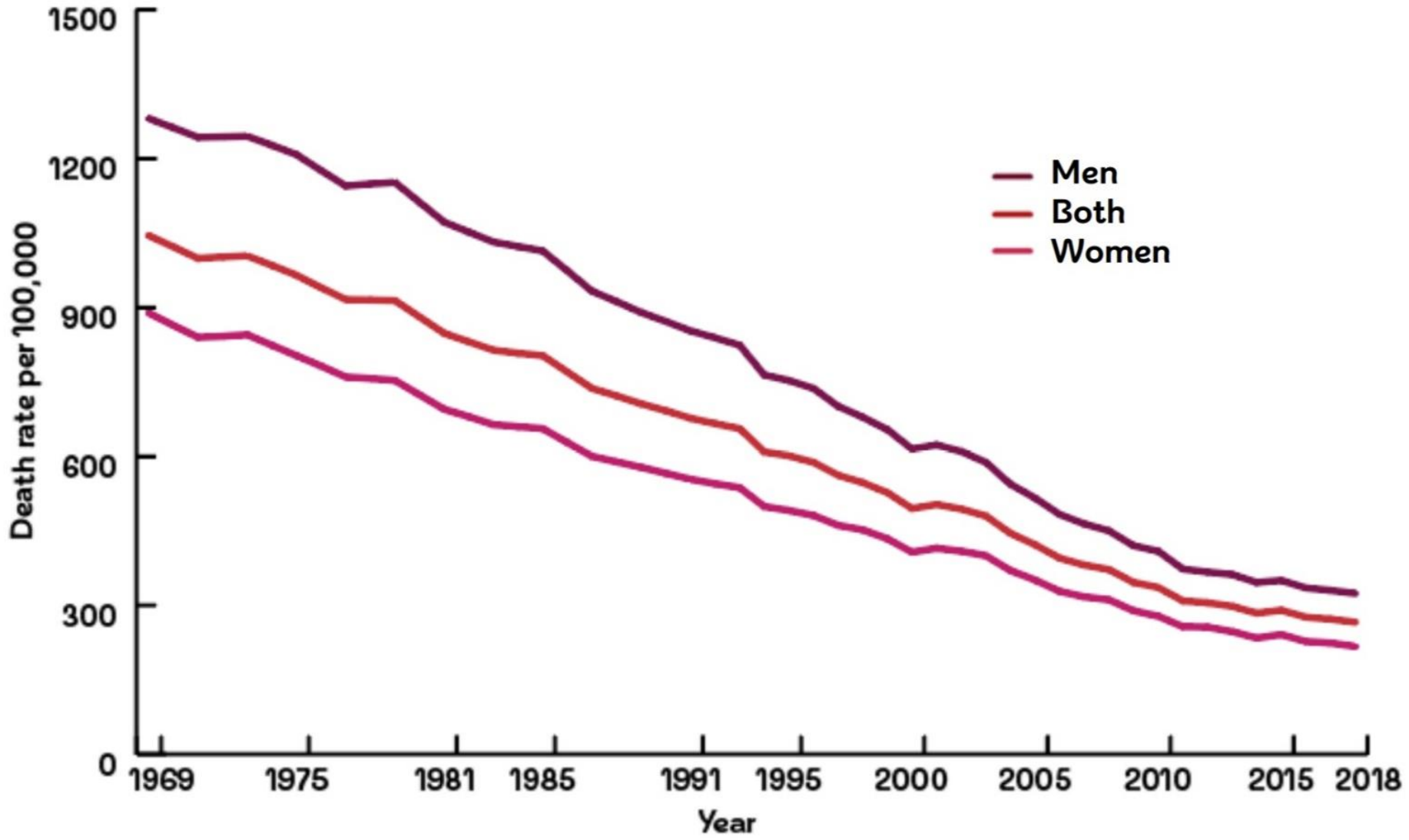
25%

of people with **Familial Hypercholesterolaemia (FH) are diagnosed and treated** optimally according to the NICE FH Guideline by 2024

The ambitions are underpinned by the need to do more to reduce health inequalities

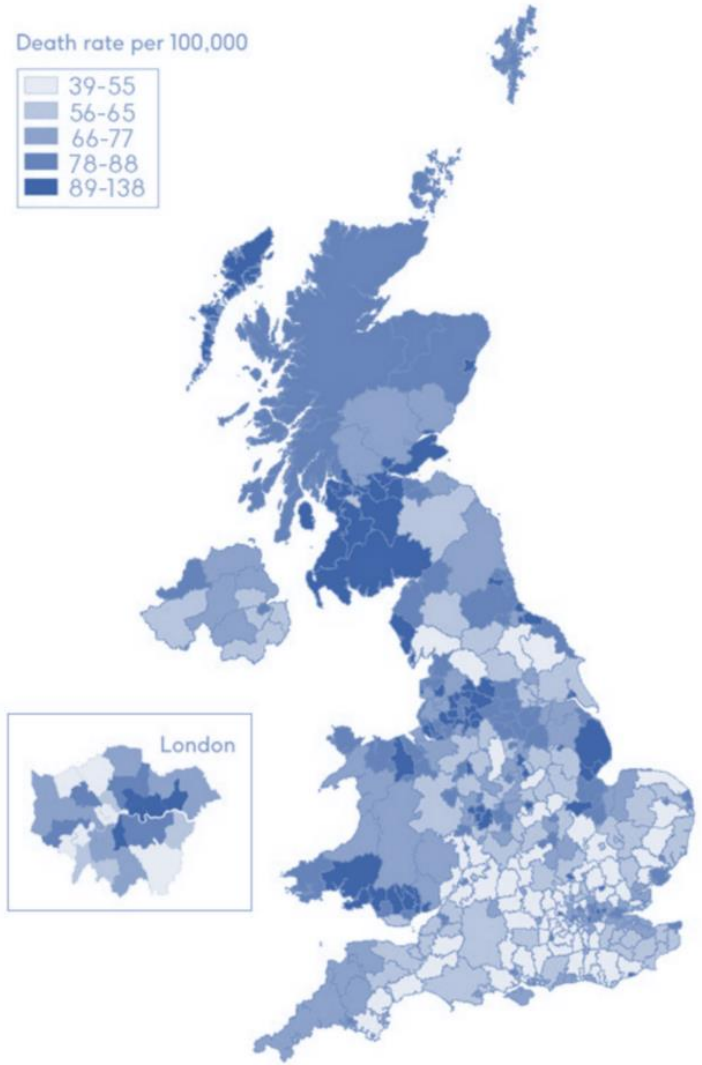
Reduce the gap significantly in amenable CVD deaths between the most and least deprived areas by 2029

Death rates from heart and circulatory diseases (CVD), UK, 1969 to 2018



British Heart Foundation Fact Sheet, July 2020

United Kingdom: Premature Mortality from CVD 2016-18

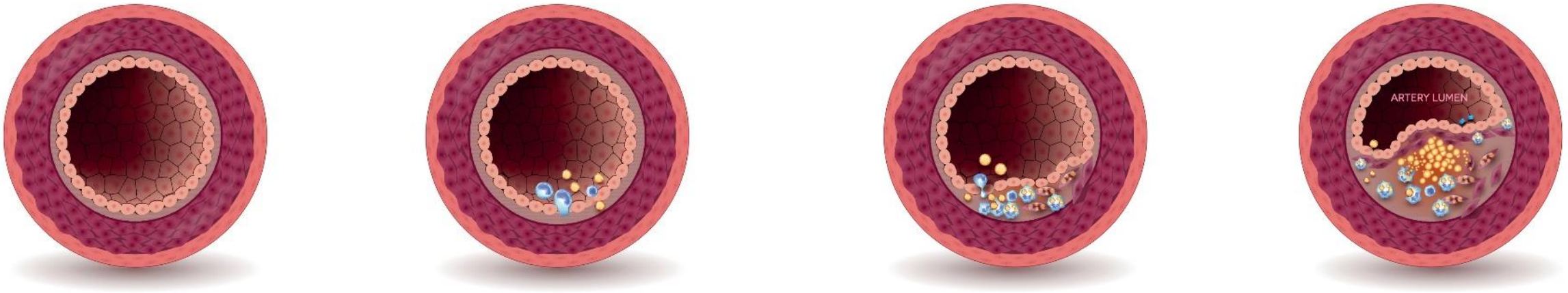


British Heart Foundation Fact Sheet, July 2020

Risk Factors

Non-Modifiable
Age
Male
Genetics (Ethnicity & Family Hx)

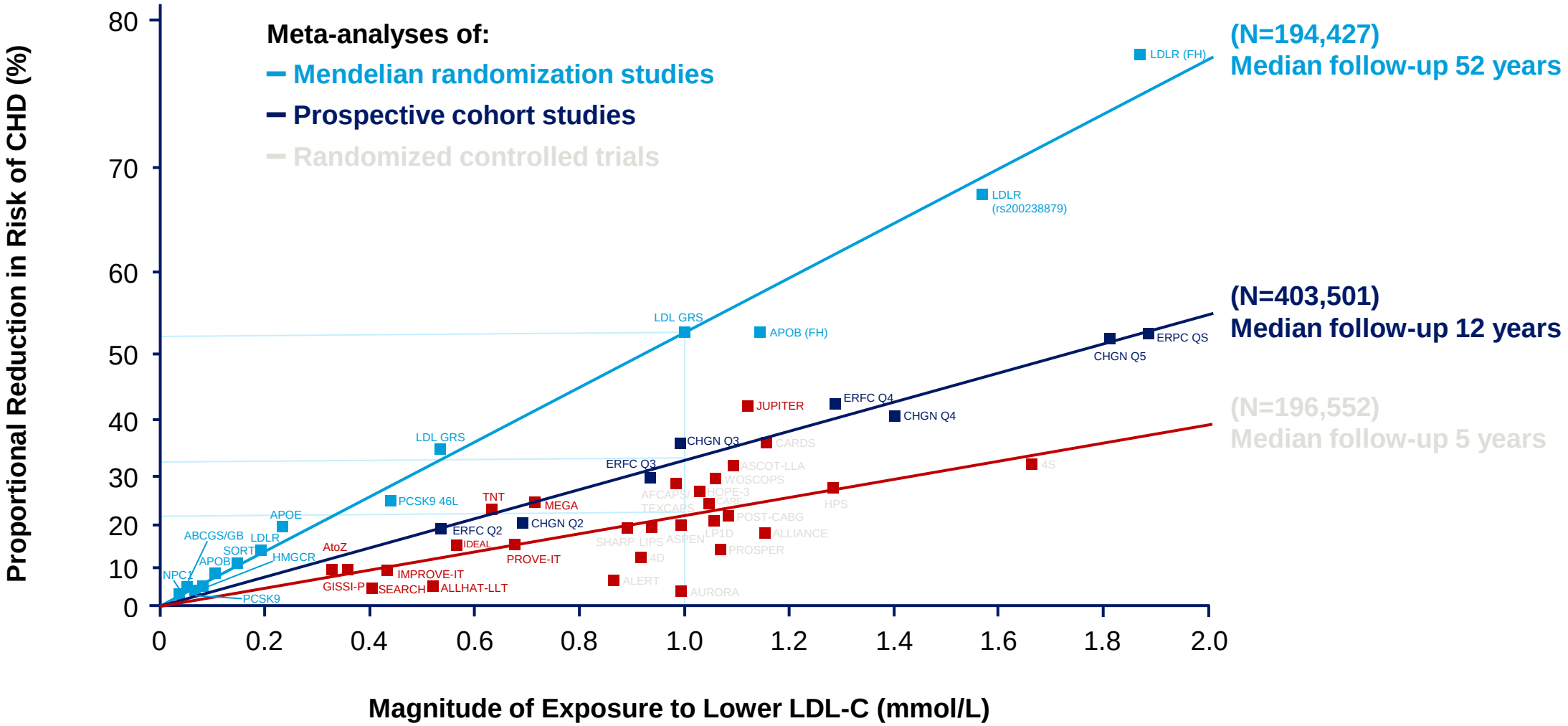
Modifiable
Lifestyle: smoking, lack of exercise, diet
Central Obesity
Chronic Kidney Disease
Diabetes
Hypertension
Lipids



1. NORMAL ARTERY
2. ENDOTHELIAL DISFUNCTION
3. FATTY STREAK FORMATION
4. STABLE (FIBROUS) PLAQUE FORMATION

Jacob Fog Bentzon. Circulation Research. Mechanisms of Plaque Formation and Rupture, Volume: 114, Issue: 12, Pages: 1852-1866, DOI: (10.1161/CIRCRESAHA.114.302721)

Effect of LDL-C by Magnitude and Duration of Exposure



Ference BA, et al. EAS Consensus Statement on LDL Causality. *Eur Heart J.* 2017;doi:10.1093/eurheartj/ehx144.
CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

Effective LDL-C remains a huge challenge

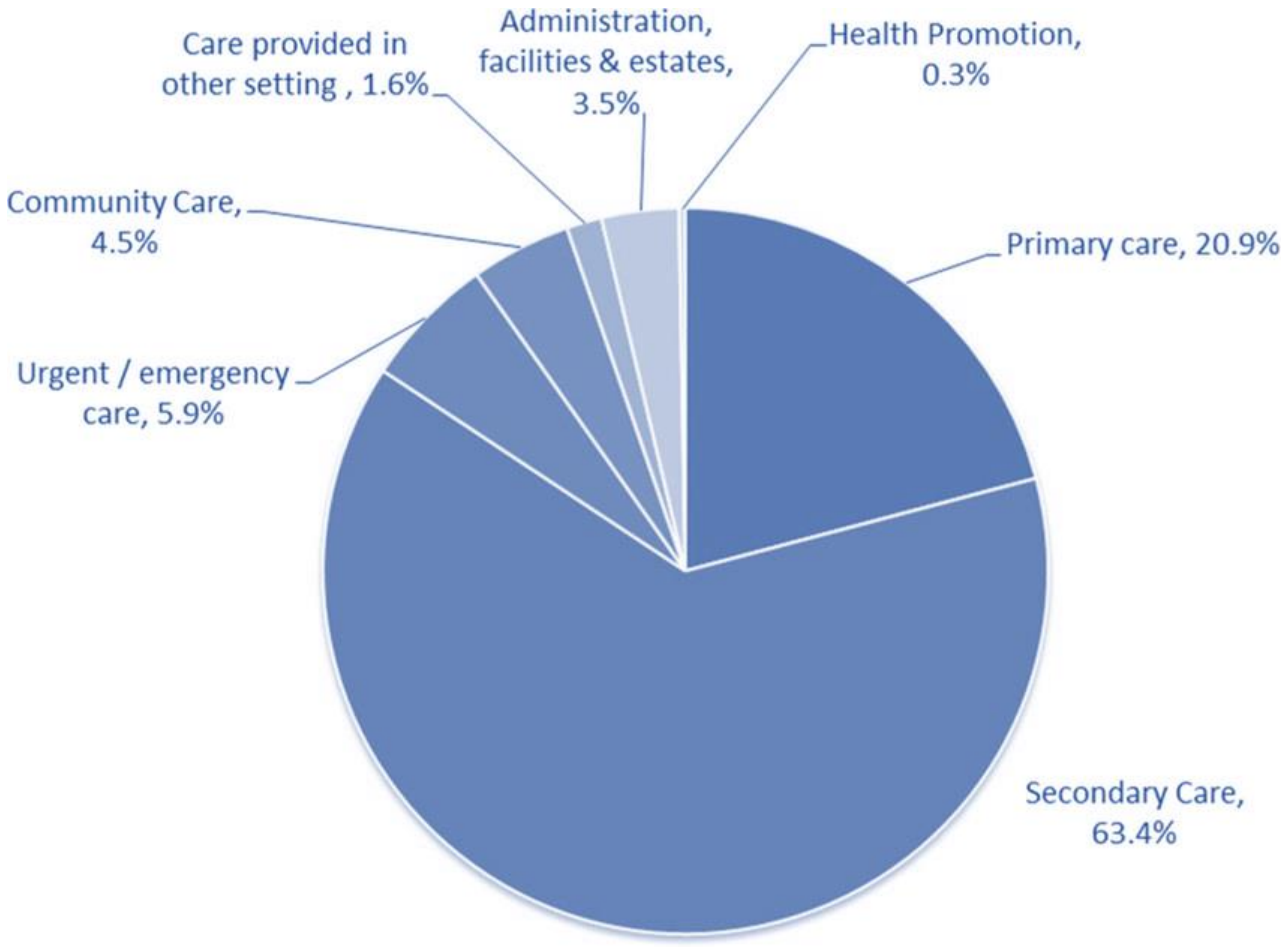
- Around 8 million patients in the UK are prescribed lipid lowering therapies (e.g. statins)
- Only 33% achieve 2019 ESC recommended LDL-C target
- The higher the baseline CV risk, the lower the likelihood of achieving LDL-C targets
- Approximately 3.5 million people in the UK have established ASCVD
  - Estimated 2.46 million have an LDL-C > 1.4mmol/L
- **Greater utilisation of adjunctive therapies is needed for more patients to achieve recommended LDL-C targets**

* Data from an 18-country, European-wide, cross-sectional, observational study of patients prescribed lipid-lowering therapy for primary or secondary prevention in primary or secondary care across Europe, including the UK (N=5,888).[1,3]

CI – confidence interval; ESC/EAS – European Society of Cardiology/European Atherosclerosis Society; LDL-C – low-density lipoprotein cholesterol

References: 1. Ray KK et al. Eur J Prev Cardiol 2020 [DOI: 10.1093/eurjpc/zwaa047]. 2. BHF. https://www.bhf.org.uk/what-we-do/our-research/heart-statistics [Accessed: September 2021].
3. Ray KK et al. Eur J Prev Cardiol 2020 [DOI: 10.1093/eurjpc/zwaa047] (supplementary data) 4. . Steen et al. BMJ Open 2017;7(2):e013255. 5. Mach F et al. Eur Heart J 2020;41(1):111-188.

NHS Expenditure on Cardiovascular Disease



Percentage of National Health Service (NHS) expenditure on cardiovascular disease by care setting, England 2012/2013. Expenditure data included are taken from the 2012–2013 programme budgeting returns. Programme budgeting returns are based on a subset of primary care trust (PCT) accounts data and represent a subset of overall NHS expenditure data. Estimates of expenditure are calculated using price paid for specific activities and services purchased from healthcare providers. PCTs follow standard guidance, procedures and mappings when calculating programme budgeting data. Adapted from NHS England—Analytical services—Programme Budgeting Team (2014) 2012/2013 Programme Budgeting Benchmarking Tool. http://www.england.nhs.uk/resources/resources-for-ccgs/prog-budgeting

Tackling Cholesterol Together

TheAHSNNetwork ACCELERATED ACCESS COLLABORATIVE HEART UK THE CHOLESTEROL CHARITY NHS

Imperial College London

04

Inclisiran- what is it, how does it work and in whom do I use it ?

Prof. Kausik K Ray

President European Atherosclerosis Society

NIHR ARC National Lead for CVD

Chief Clinical Officer and Trials Lead DISCOVER NOW, HDR UK Innovation Hub NW London

Professor of Public Health and Consultant Cardiologist

Director of the Imperial Centre for Cardiovascular Disease Prevention

Director of Imperial Clinical Trials Unit-Global, Imperial College London

Disclosures

- **Research grants:** Amgen, Sanofi, Regeneron, MSD, Pfizer, Daiichi Sankyo

- **Consultancy:** Amgen, Sanofi, Regeneron, MSD, Pfizer, Astra Zeneca, Lilly, Medicines Company, Kowa, IONIS, Takeda, Novo Nordisk, Boehringer Ingelheim, Esperion, Cipla, Algorithm, Abbvie, Resverlogix, Cerenis , Novartis, Silence Therapeutics, New Amsterdam, Bayer, Novartis

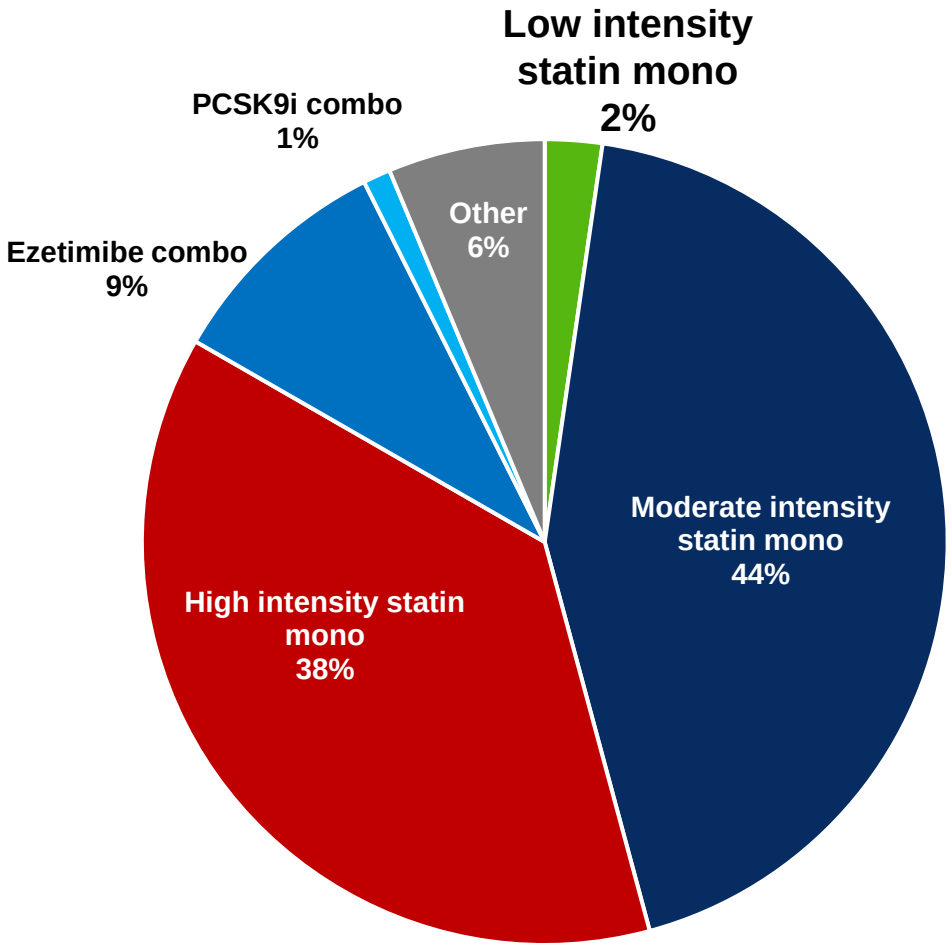
Start with risk assessment and then treat to risk:
New Lower Targets For Those At Highest Risk

Recommendations	Class[a]	Level[b]
In secondary prevention patients at VERY HIGH-risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended.[34-36, 121, 122]	I	A
In primary prevention, for individuals at VERY HIGH-risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended.[34-36, 121, 122]	I	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) whilst taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (40 mg/dL) may be considered.[121, 122]	IIb	B
In patients at HIGH-risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (70 mg/dL) are recommended.[35, 36]	I	A
In individuals at MODERATE-risk[c], an LDL-C goal of <2.6 mmol/L (100 mg/dL) should be considered.[35]	IIa	A
In individuals at LOW-risk[c] an LDL-C goal <of 3.0 mmol/L (115 mg/dL) may be considered.[35]	IIb	A

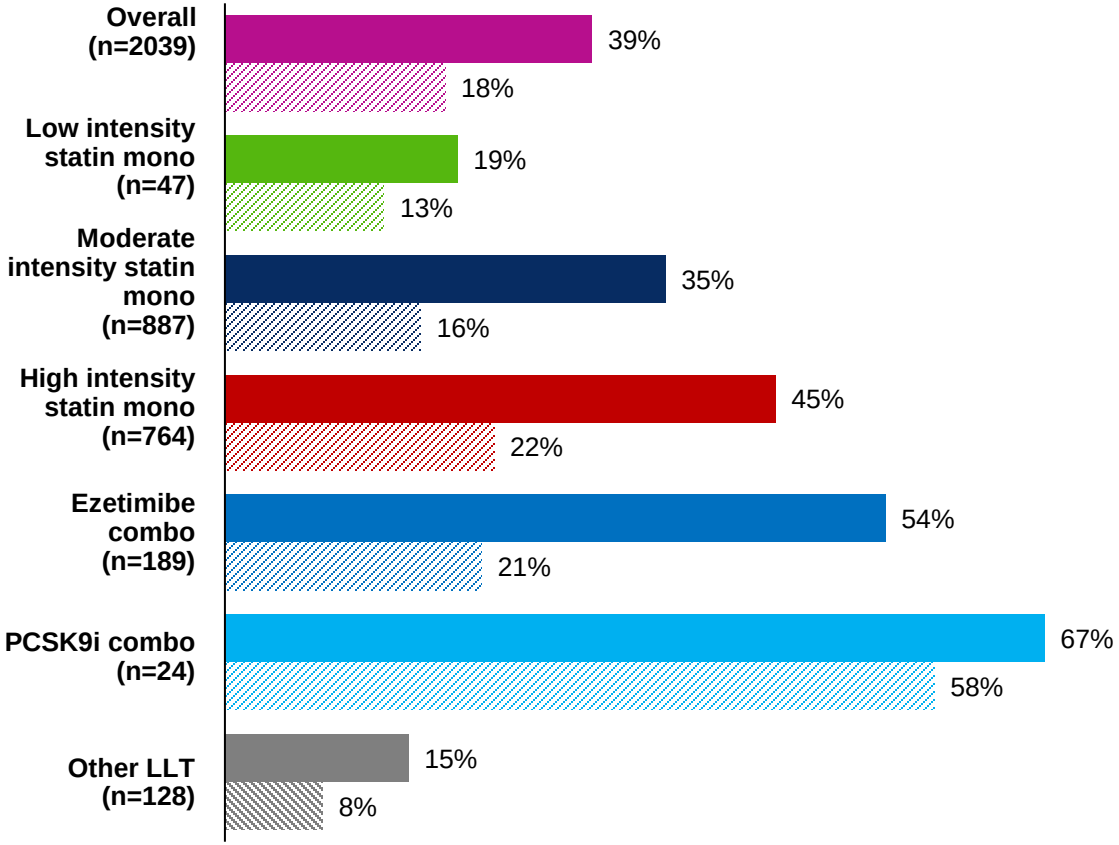
Starting LDL-C, mmol/L (mg/dL)	LDL-C goals, mmol/L (mg/dL)
	50%
6.2 (240)	<3.1 (120)
5.9 (230)	<3.0 (115)
5.7 (220)	<2.8 (110)
5.4 (210)	<2.7 (105)
5.2 (200)	<2.6 (100)
4.9 (190)	<2.5 (95)
4.7 (180)	<2.3 (90)
4.4 (170)	<2.2 (85)
4.1 (160)	<2.1 (80)
3.9 (150)	<1.9 (75)
3.6 (140)	<1.8 (70)
3.4 (130)	<1.7 (65)
3.1 (120)	<1.6 (60)
2.8 (110)	<1.4 (55)
2.6 (100)	<1.3 (50)
2.3 (90)	<1.2 (45)
2.1 (80)	<1.0 (40)
1.8 (70)	<0.9 (35)

LDL-C goal attainment by LLT in patients with established ASCVD

LLT use among patients with established ASCVD



2016/2019 goal attainment in patients with established ASCVD



Pie chart shows % of patients receiving each LLT at LDL-C measurement. Bar chart shows % of patients achieving 2016 (solid bars) and 2019 (hashed bars) LDL-C goals.
mono, monotherapy.

Ray KK, et al. Eur J Prev Cardiol 2020;Epub ahead of print.

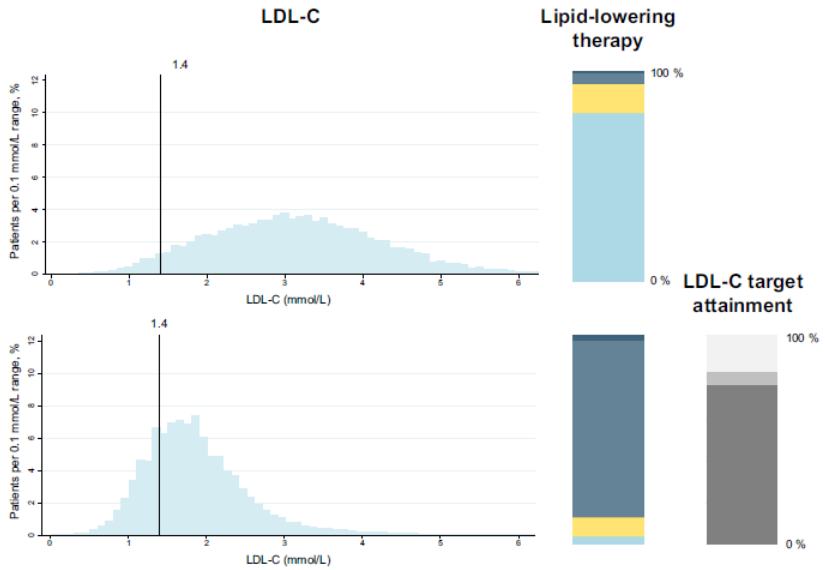
Simulation of Potential Goal attainment if treatments optimised in SWEDEHEART*

Observed

At/during admission for MI

↓

6-10 weeks after MI

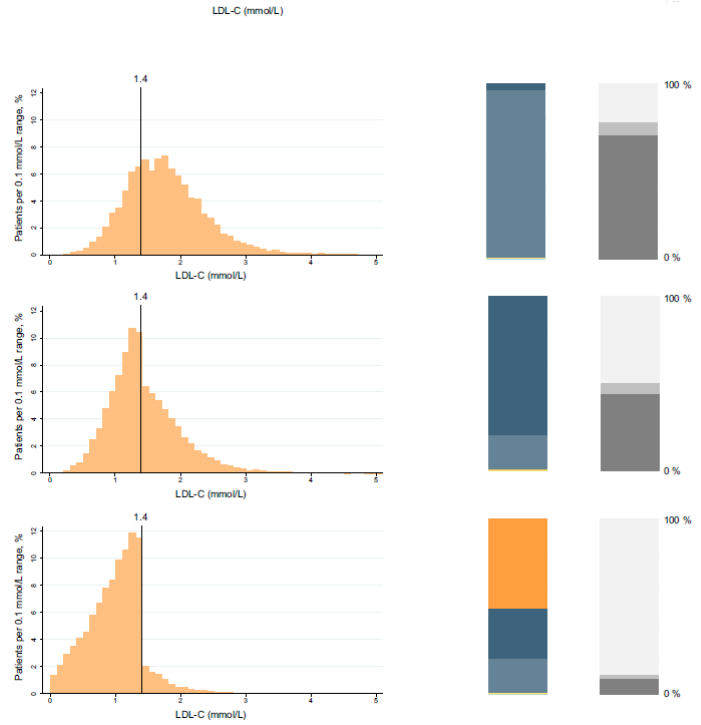


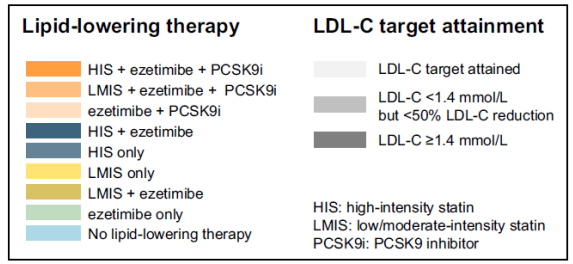
Simulated

Add/uptitrate to high-intensity statin

Add ezetimibe

Add PCSK9 inhibitor





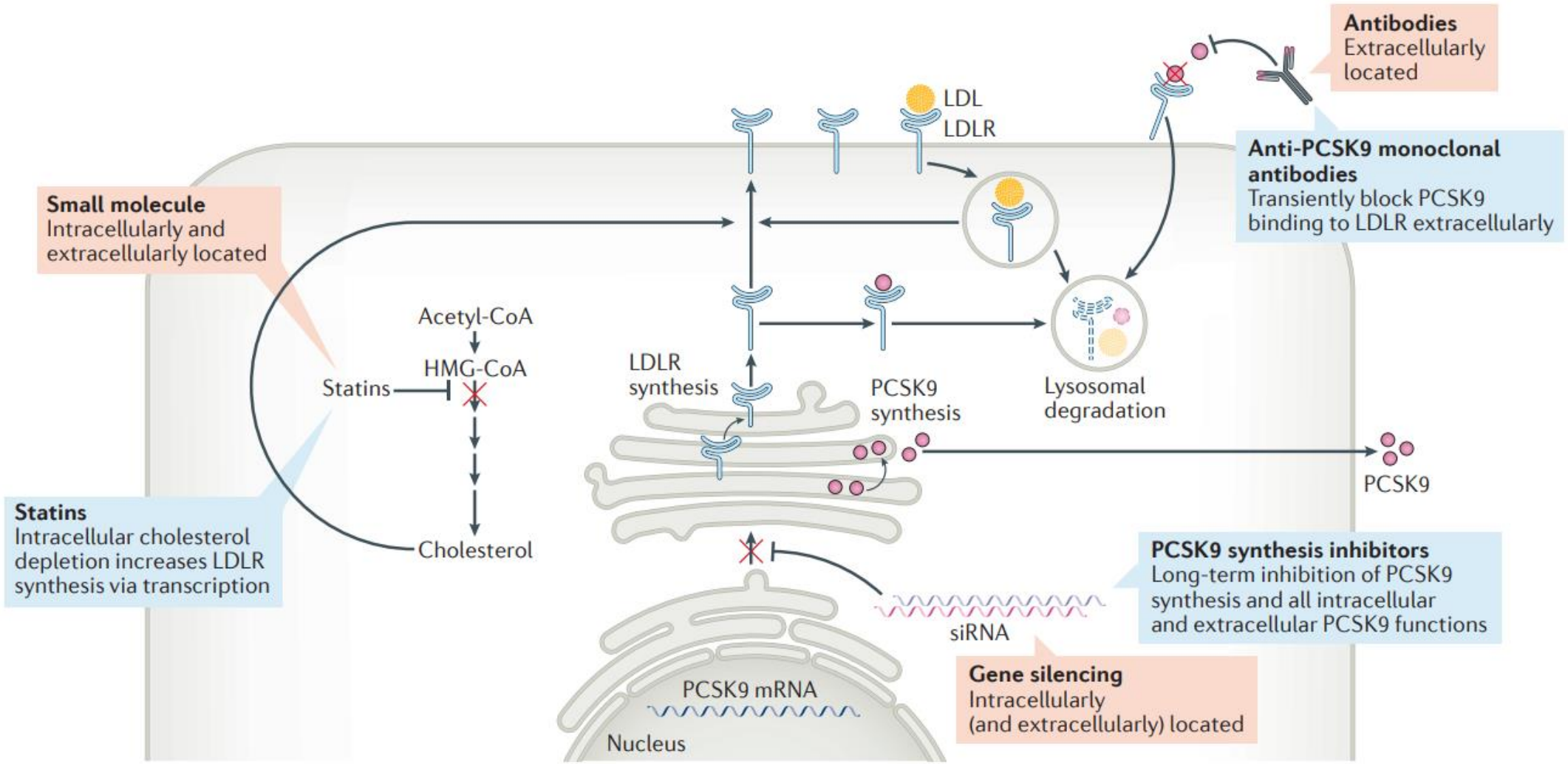
Four out of five patients with a recent MI would be eligible for escalated LTT according to the 2019 ESC/EAS guidelines at 6–10 weeks after the event

- 50% of those patients would be eligible for additional treatment with a PCSK9i after Maximum Tolerated Dose of statin and ezetimibe treatment

Allahyari A, et al. Eur Heart J. 2020;41:3900–9
MI, myocardial infarction; MTD, maximum-tolerated dose

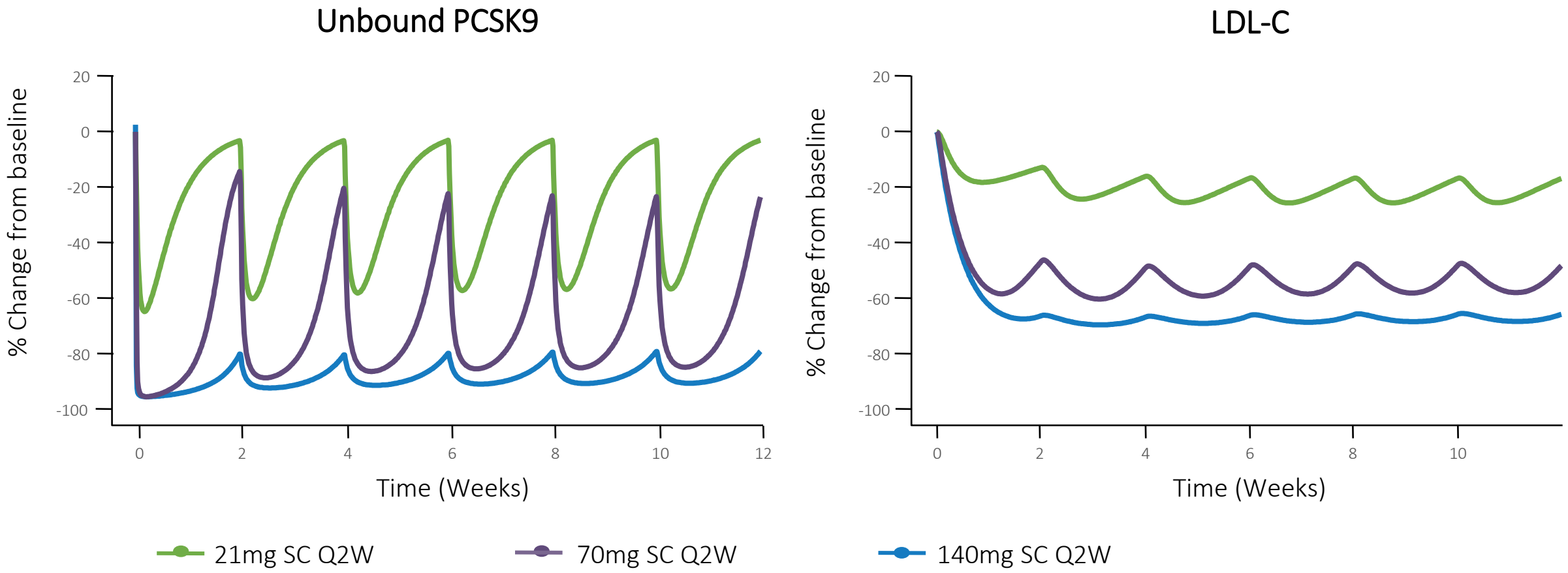
*All patients in SWEDEHEART, aged 18–74 years, admitted with an MI between 1 January 2013 and 1 October 2017, and who survived until discharge, were included in the study

Therapeutic approaches to reducing LDL-C via the LDL receptor **Small Molecules, Mabs, siRNA**



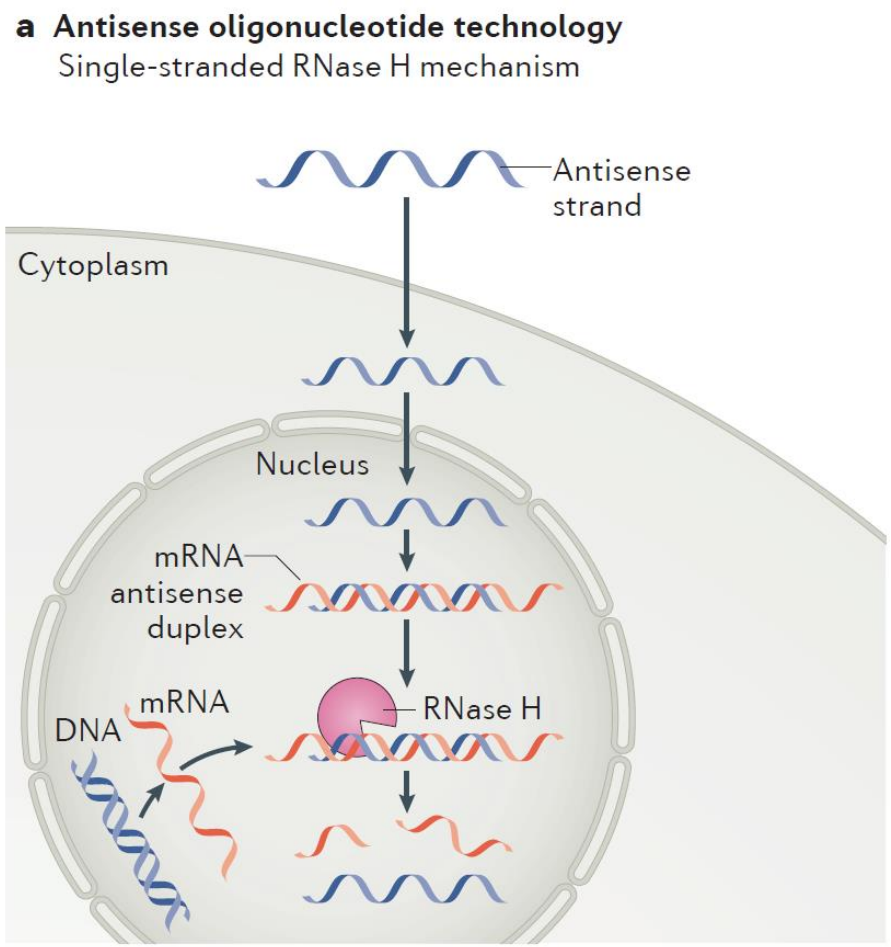
Nordestgaard B, Ray KK et al. Nature Reviews Cardiology 2018;15:261–272

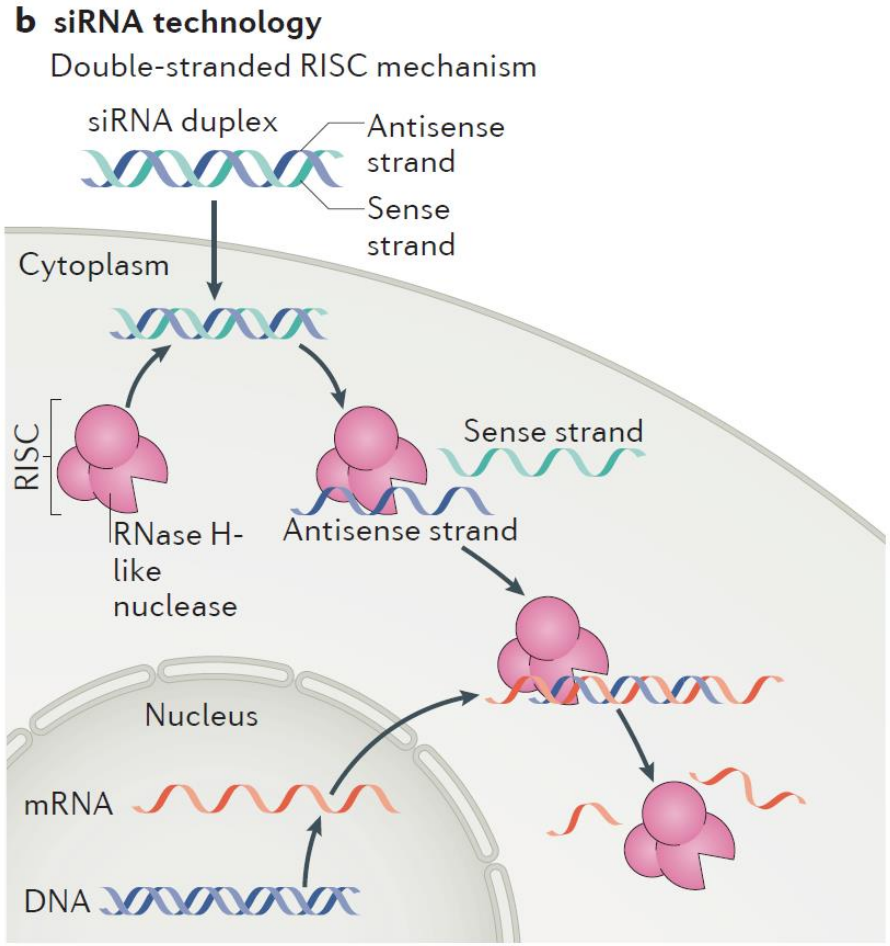
Sustained PCSK9 inhibition with 140 mg Q2W evolocumab leads to effective, stable LDL-C reduction



http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM452354.pdf. Accessed 25 Feb 2016.

RNA based approaches



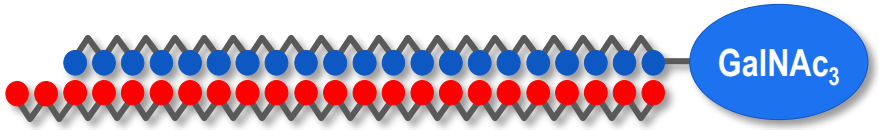


1. Nordestegaard B, Ray KK Nature Reviews Cardiology Jan 2018

GalNAc-siRNA conjugates facilitate rapid hepatic uptake

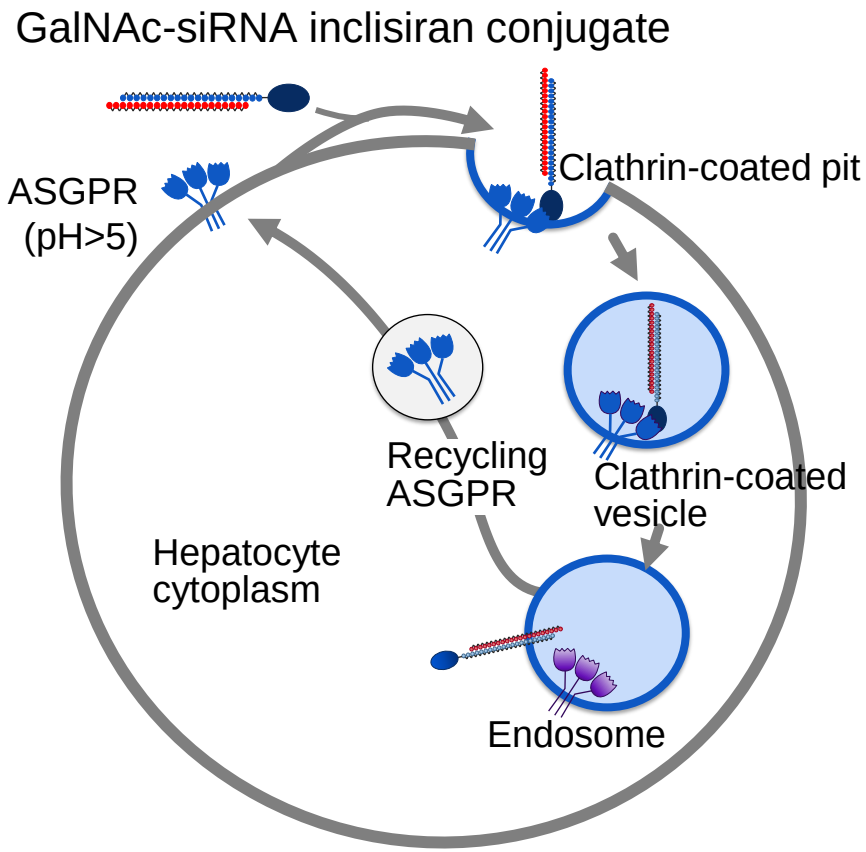
Asialoglycoprotein receptor (ASGPR)

- Highly expressed in hepatocytes only
- High rate of uptake

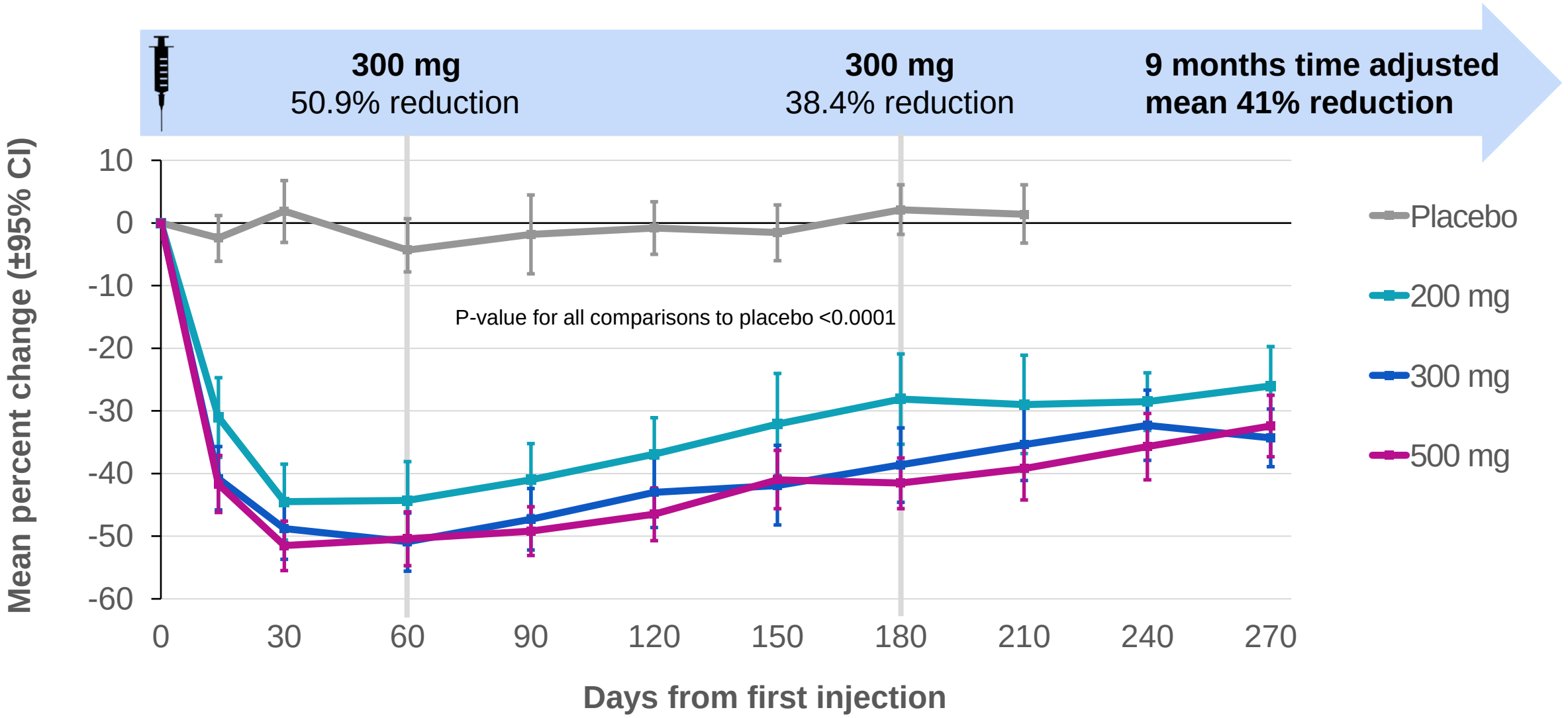


Inclisiran

- siRNA conjugated to N-acetylgalactosamine
- Subcutaneous administration
- Targeted delivery to hepatocytes

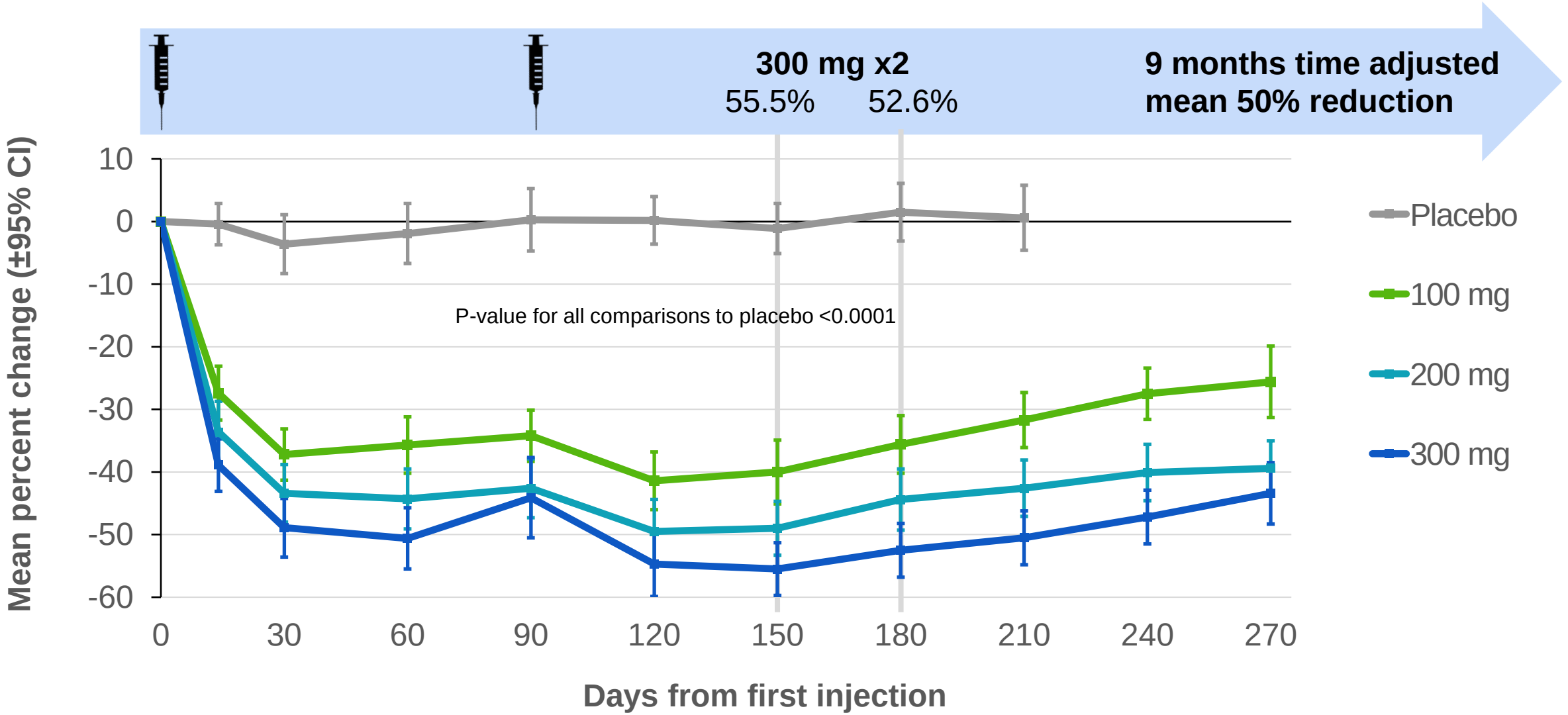


Efficacy: One dose starting regimen **Robust, sustained LDL-C reductions – 300 mg optimal**



1. Ray KK et al. N Engl J Med 2017; 376:1430-144

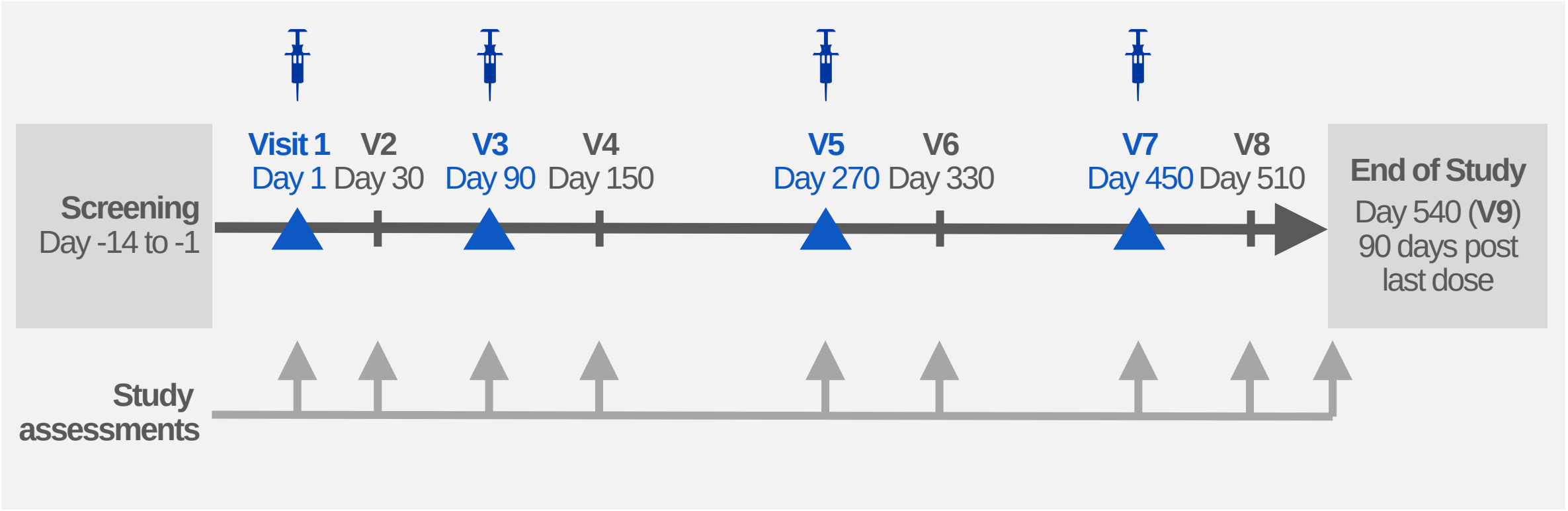
Efficacy: Two dose starting regimen **Robust, sustained LDL-C reductions – optimal start regimen**



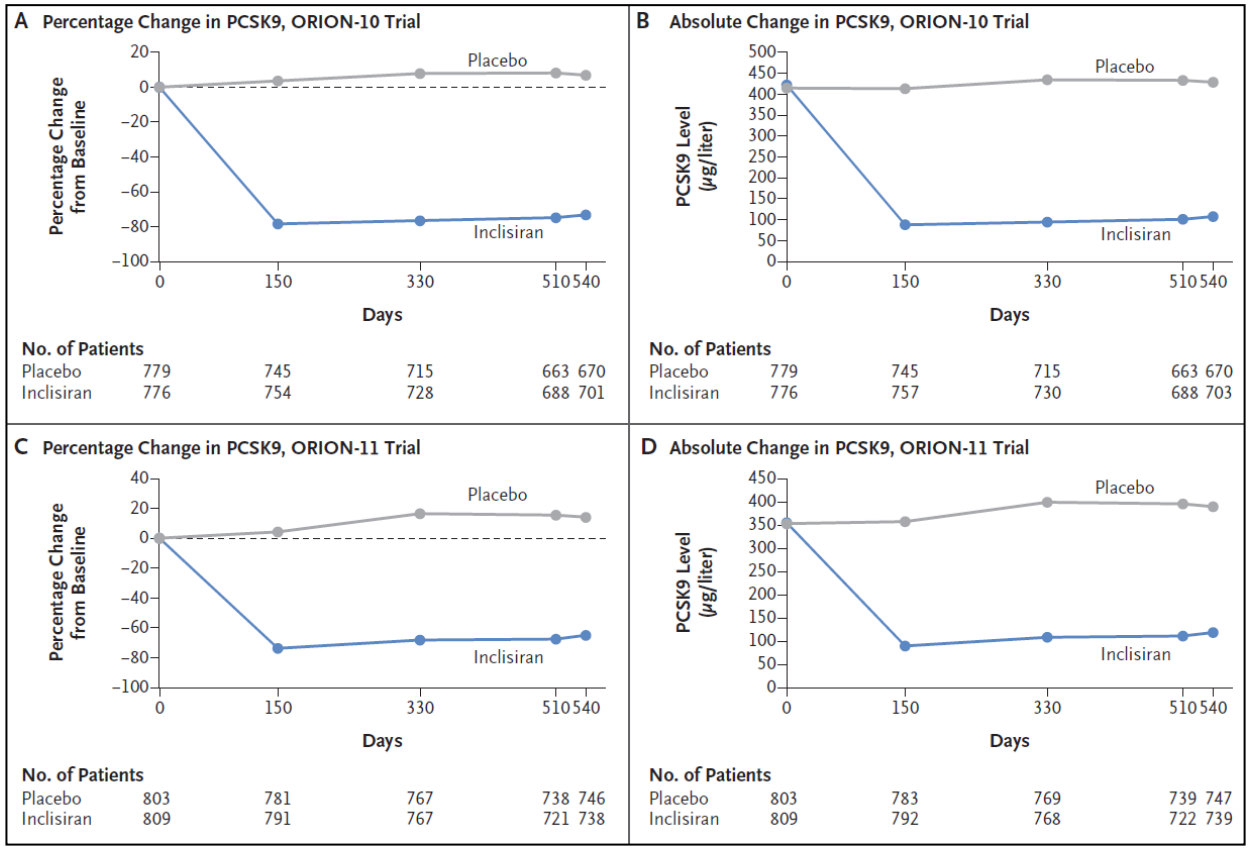
1. Ray KK et al. N Engl J Med 2017; 376:1430-144

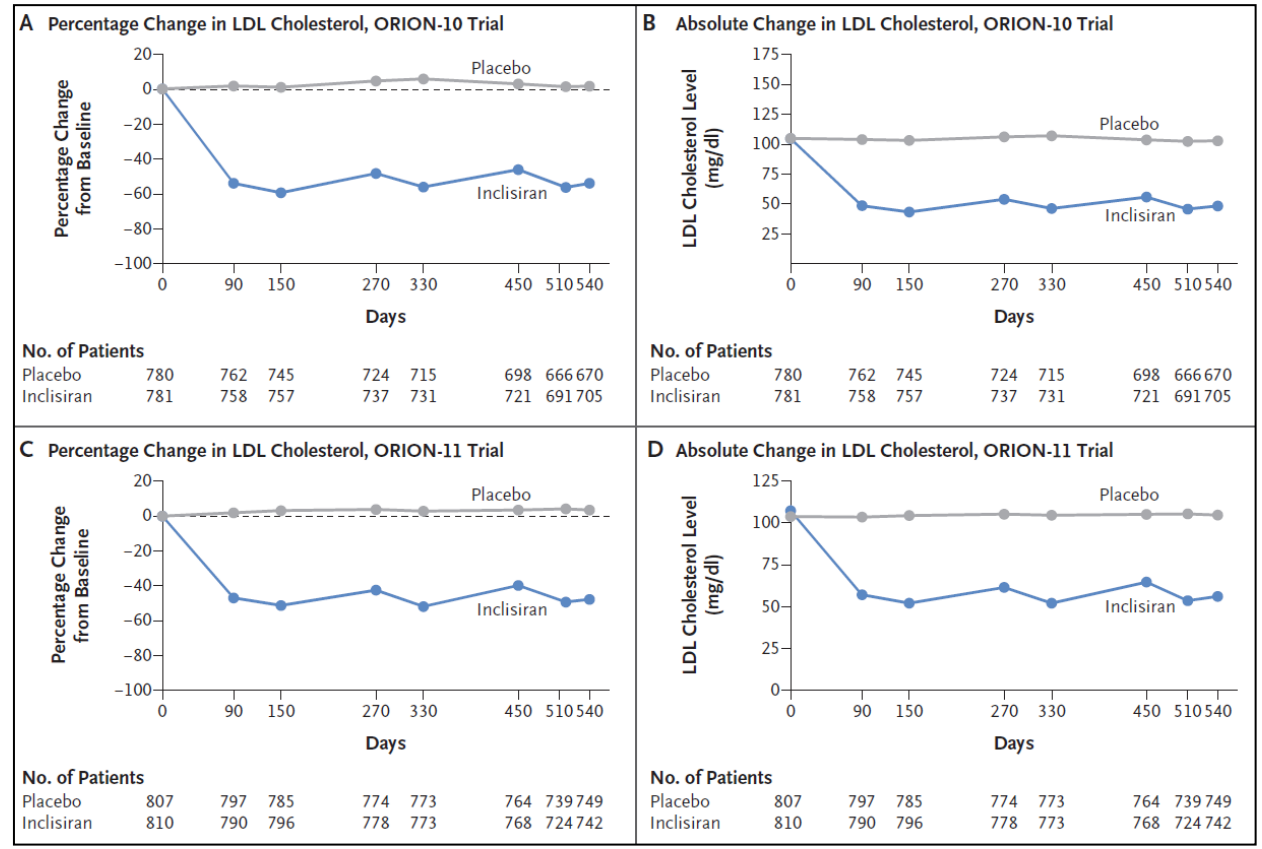
ORION-9,10,11: Study design
Eighteen months treatment and observation

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



Efficacy and safety of inclisiran in ORION 10 and 11





Ray KK et al. N Engl J Med 2020;382:1507–1519

ORION 9 Efficacy in HeFH

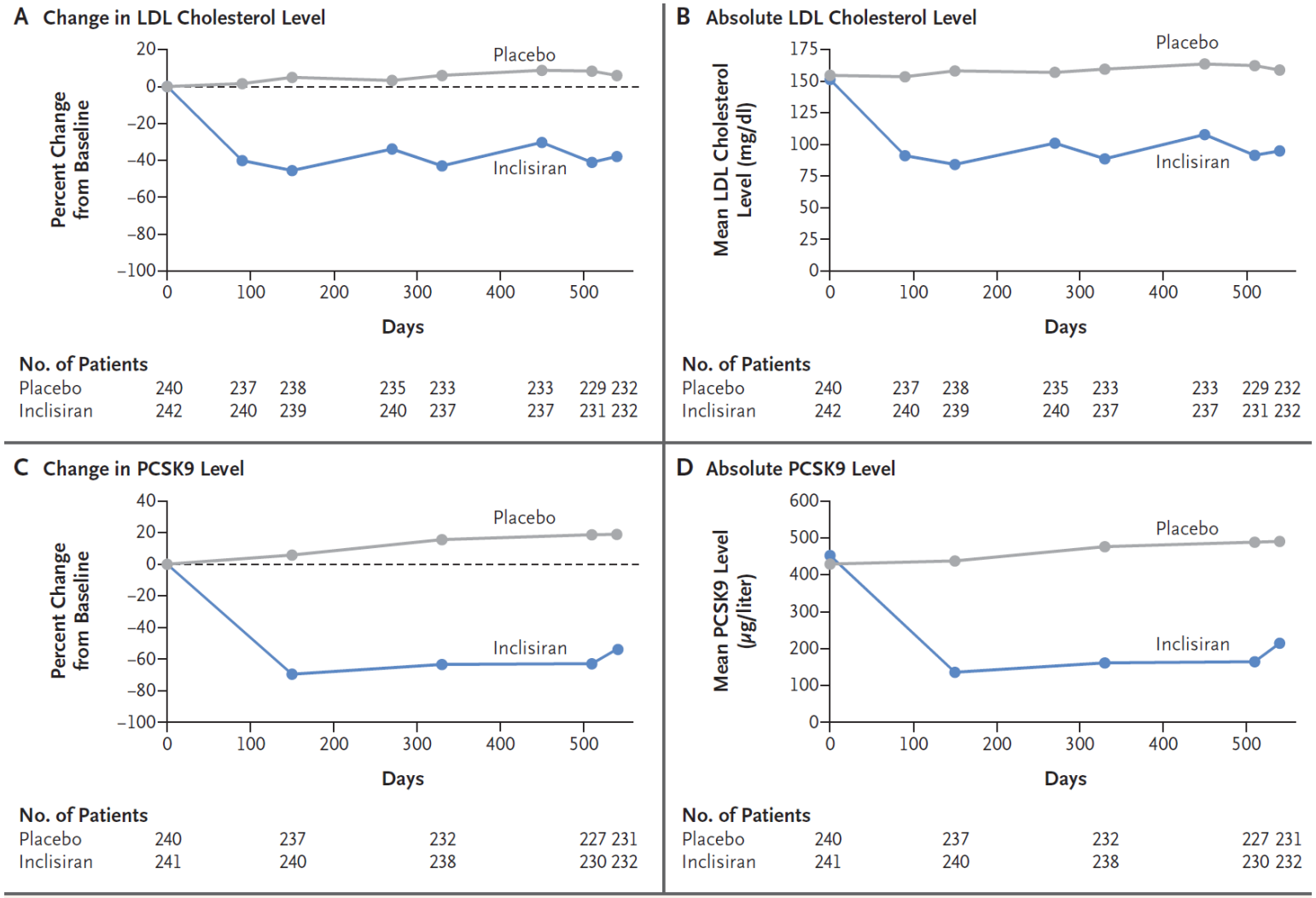


Figure 1. Percent and Absolute Changes in Low-Density Lipoprotein (LDL) Cholesterol and PCSK9 Levels during the 540-Day Trial Period (Intention-to-Treat Population).

Raal D, Ray KK et al. N Engl J Med 2020;382:

Safety: ORION 10 and 11

Parameter	ORION-10		ORION-11	
	Placebo (n=778)	Inclisiran (n=781)	Placebo (n=804)	Inclisiran (n=811)
AEs, n (%)	582 (74.8)	574 (73.5)	655 (81.5)	671 (82.7)
≥1 Event leading to treatment discontinuation	17 (2.2)	19 (2.4)	18 (2.2)	23 (2.8)
≥1 Serious AE, n (%)	205 (26.3)	175 (22.4)	181 (22.5)	181 (22.3)
Fatal AE	11 (1.4)	12 (1.5)	15 (1.9)	14 (1.7)
Death from CV causes	5 (0.6)	7 (0.9)	10 (1.2)	9 (1.1)
Cancer-related death	3 (0.4)	1 (0.1)	3 (0.4)	3 (0.4)
New, worsening, or recurrent cancer	26 (3.3)	26 (3.3)	20 (2.5)	16 (2.0)
Other CV AEs, n (%) [a]				
Prespecified exploratory cardiovascular end point	79 (10.2)	58 (7.4)	83 (10.3)	63 (7.8)
Fatal or nonfatal myocardial infarction	18 (2.3)	20 (2.6)	22 (2.7)	10 (1.2)
Fatal or nonfatal stroke	7 (0.9)	11 (1.4)	8 (1.0)	2 (0.2)
Injection-site AEs, n (%) [b]				
Any reaction	7 (0.9)	20 (2.6)	4 (0.5)	38 (4.7)
Mild	7 (0.9)	13 (1.7)	3 (0.4)	23 (2.8)
Moderate	0	7 (0.9)	1 (0.1)	15 (1.8)
Severe	0	0	0	0
Persistent	0	0	0	0

[a] The exploratory cardiovascular end point comprised a Medical Dictionary for Regulatory Activities–defined cardiovascular basket of non-adjudicated terms, including those classified within cardiac death, and any signs or symptoms of cardiac arrest, nonfatal myocardial infarction, or stroke.

[b] Injection-site adverse events included the preferred terms injection-site erythema, injection-site hypersensitivity, injection-site pruritus, injection-site rash, and injection-site reaction

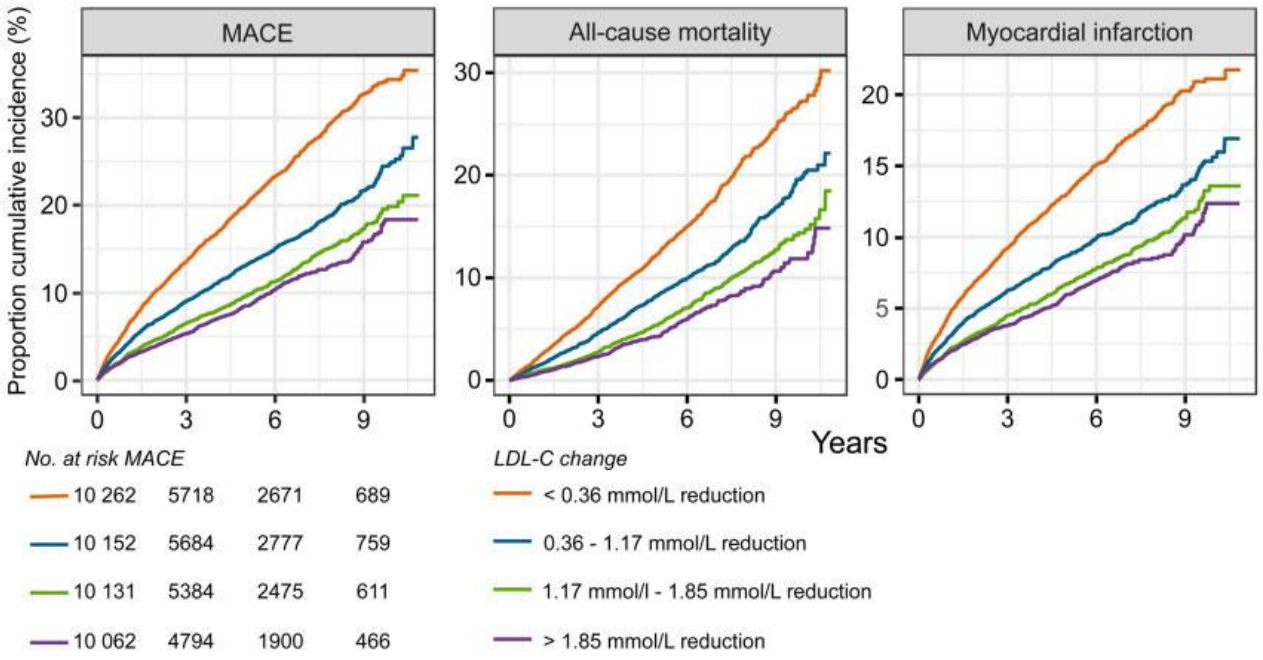
Ray KK et al. N Engl J Med 2020;382:1507–1519

Safety: ORION 10 and 11

Parameter	ORION-10		ORION-11	
	Placebo (n=778)	Inclisiran (n=781)	Placebo (n=804)	Inclisiran (n=811)
Frequent AEs, n (%)				
Diabetes mellitus	108 (13.9)	120 (15.4)	94 (11.7)	88 (10.9)
Nasopharyngitis	-	-	90 (11.2)	91 (11.2)
Bronchitis	30 (3.9)	46 (5.9)	-	-
Dyspnoea	33 (4.2)	39 (5.0)	-	-
Hypertension	42 (5.4)	42 (5.4)	54 (6.7)	53 (6.5)
Upper respiratory tract infection	33 (4.2)	39 (5.0)	49 (6.1)	52 (6.4)
Arthralgia	-	-	32 (4.0)	47 (5.8)
Osteoarthritis	-	-	40 (5.0)	32 (3.9)
Back pain	39 (5.0)	39 (5.0)	-	-
Liver function				
Alanine aminotransferase >3x ULN	2 (0.3)	2 (0.3)	4 (0.5)	4 (0.5)
Aspartate aminotransferase >3x ULN	5 (0.6)	4 (0.5)	4 (0.5)	2 (0.2)
Alkaline phosphatase >3x ULN	3 (0.4)	5 (0.6)	2 (0.2)	1 (0.1)
Bilirubin >2x ULN	3 (0.4)	4 (0.5)	8 (1.0)	6 (0.7)
Kidney function: creatinine >2 mg/dL	30 (3.9)	30 (3.8)	11 (1.4)	5 (0.6)
Muscle: creatine kinase >5x ULN	8 (1.0)	10 (1.3)	9 (1.1)	10 (1.2)
Hematology: platelet count <75x10^9/L	0	1 (0.1)	1 (0.1)	0

Ray KK et al. N Engl J Med 2020;382:1507–1519

CV events and patient characteristics across quartiles of absolute LDL-C reduction



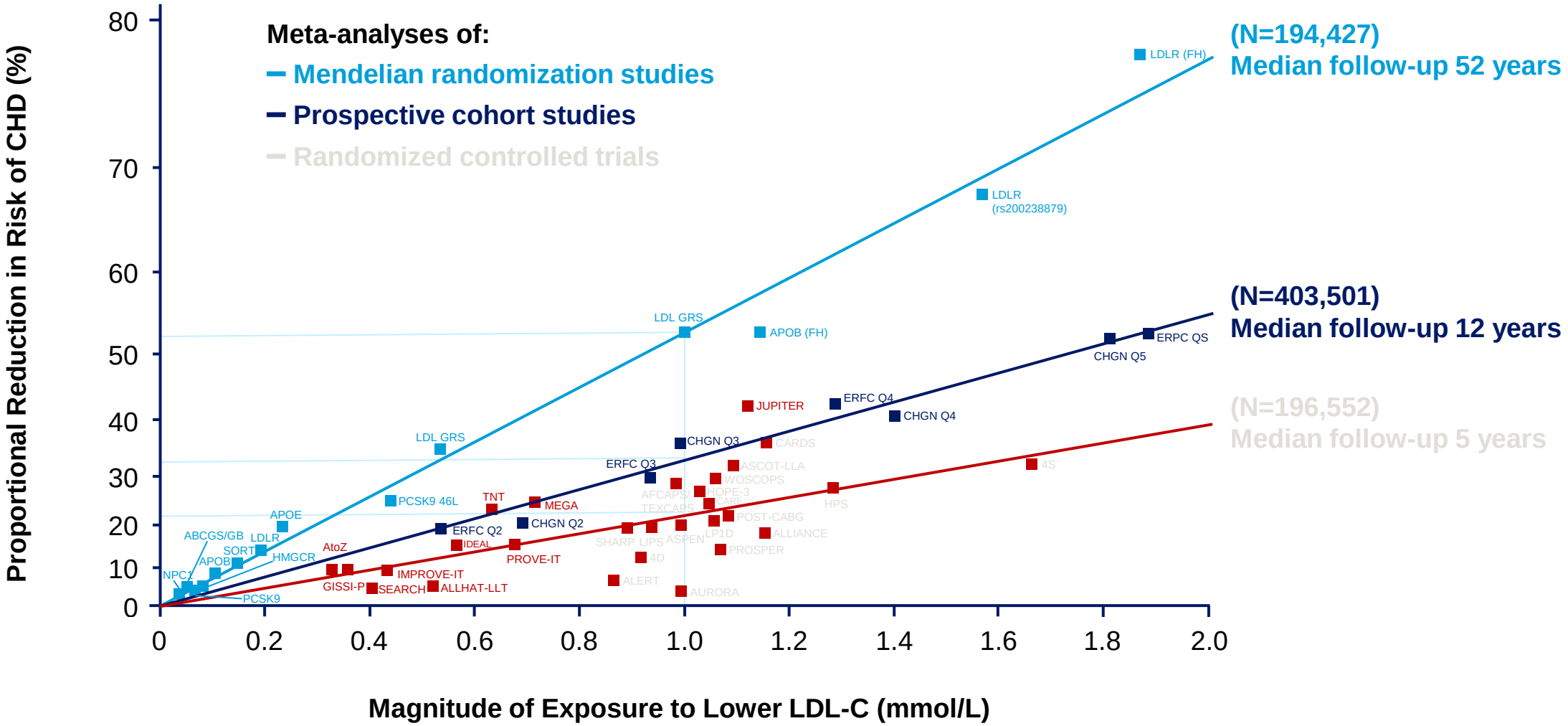
	LDL-C Reduction from index event to CR visit (mmol/L)			
	<0.36	0.36–1.17	1.17–1.85	>1.85
Age (years)	66 (59–71)	64 (57–69)	63 (56–69)	62 (55–68)
Hypertension	54%	43%	37%	34%
Diabetes mellitus	32%	20%	13%	12%
Prior MI	27%	12%	6%	4%
LDL-C at admission (mmol/L)	2.1 (1.7–2.7)	2.8 (2.3–3.2)	3.4 (3.0–3.8)	4.3 (3.8–4.8)
Statin at admission				
No statin	42%	76%	94%	96%
Low intensity	4%	2%	1%	<1%
Medium intensity	45%	19%	5%	3%
High intensity	9%	3%	1%	1%
LDL-C at CR visits (mmol/L)	2.3 (1.8-2.9)	1.9 (1.5-2.4)	1.9 (1.5-2.2)	1.8 (1.5-2.2)

Patients in quartile 1 appear to have more comorbidities, to be at higher risk of CV events and to have highest rates of prior statin treatment (58%).

LLT remained the same, but LDL-C levels changed

Schubert, Jessica, et al. *European heart journal* 42.3 (2021): 243-252.

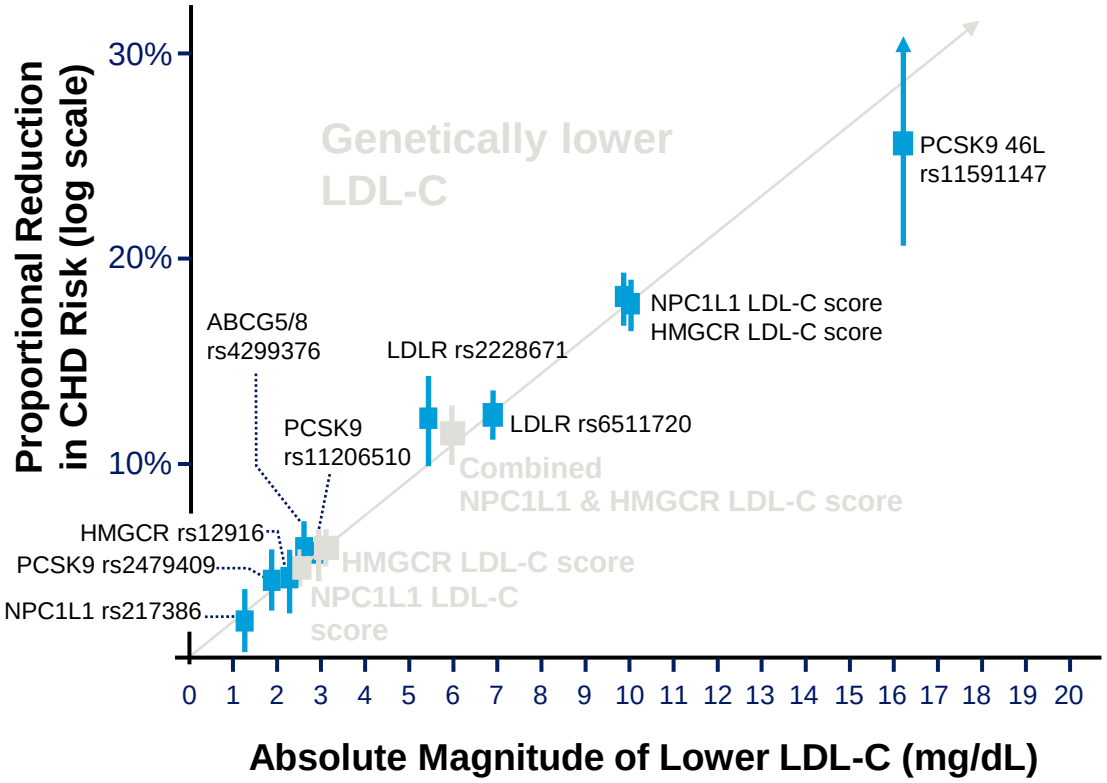
Effect of LDL-C by Magnitude and Duration of Exposure



Ference BA, et al. EAS Consensus Statement on LDL Causality. *Eur Heart J.* 2017;doi:10.1093/eurheartj/ehx144.
CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

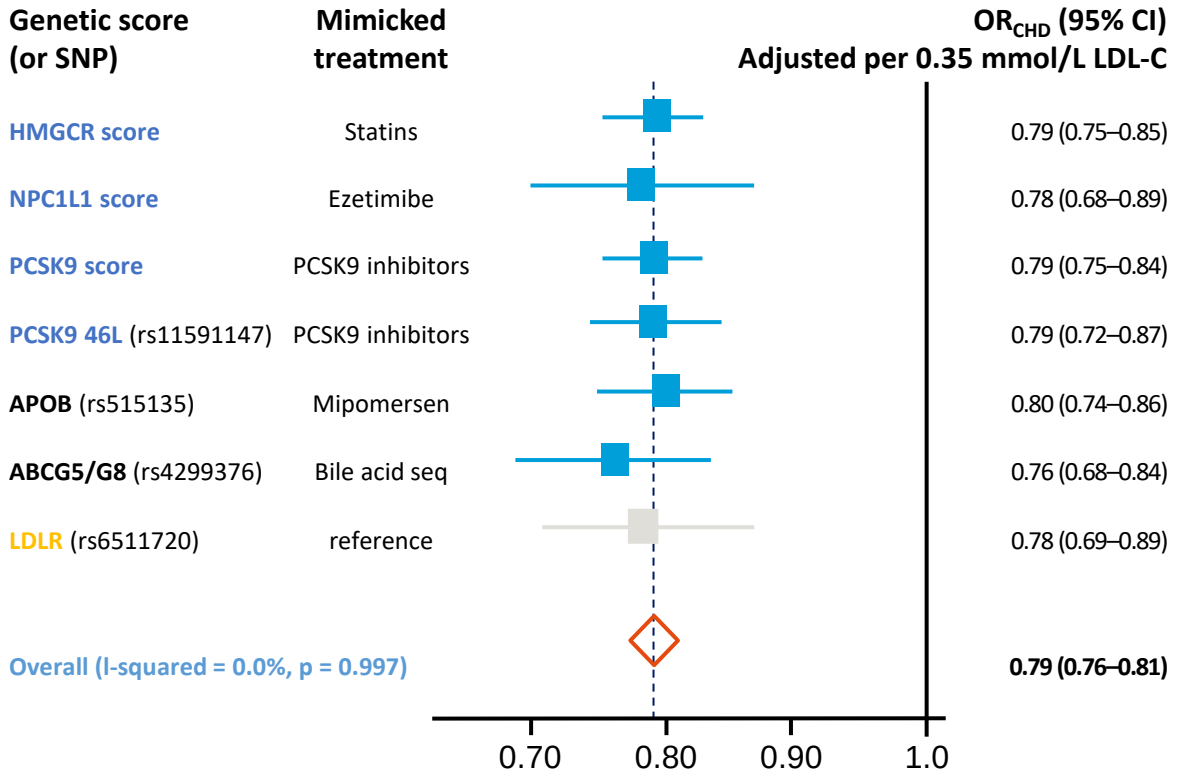
Evidence from Mendelian Randomization Studies

Log-linear Association Between Genetically and Pharmacologically Mediated Lower LDL-C and Risk of CHD



Ference BA, et al. *J Am Coll Cardiol.* 2012;60:2631–9.
Ference BA, et al. *J Am Coll Cardiol.* 2015;65:1552–61.

Effect of Exposure to Lower LDL-C by Mechanism of LDL-C Lowering: Effects of Genetic Variants or Genetic Score



Ference BA, et al. EAS Consensus Statement on LDL Causality. *Eur Heart J*. 2017; doi:10.1093/eurheartj/ehx144

ABCG5/G8 = ATP binding cassette subfamily G member 5/8; APOB = apolipoprotein B; CHD = coronary heart disease; CI = confidence interval; HMGCR = 3-hydroxy-3-methylglutaryl-CoA reductase; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; NPC1L1 = Niemann-pick C1-like 1; OR = odds ratio; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Tackling Cholesterol Together

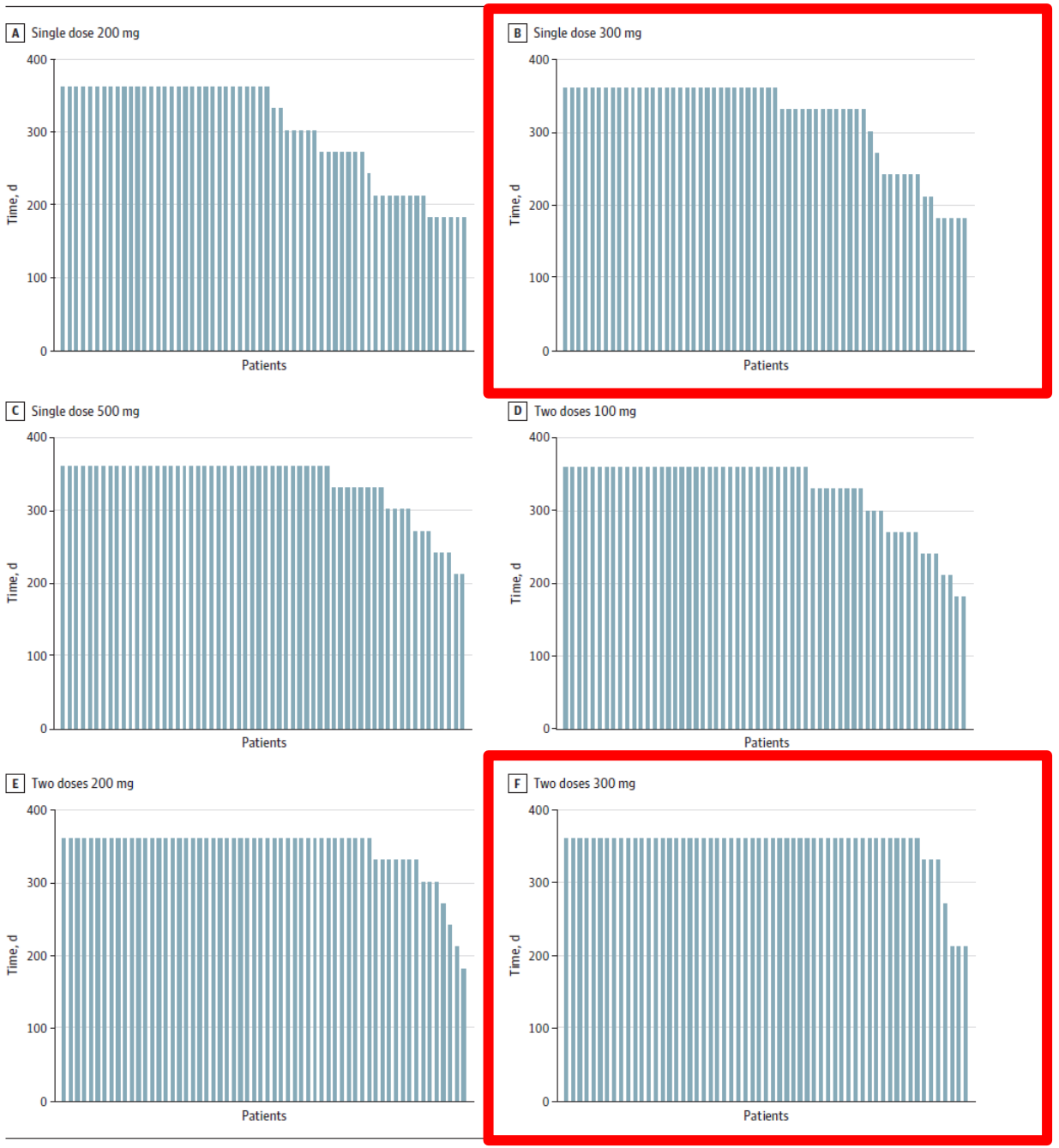
JAMA Cardiology | Original Investigation

Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels

One-Year Follow-up of the ORION-1 Randomized Clinical Trial

Kausik K. Ray, FRCP; Robert M. Stoekenbroek, MD; David Kallend, FRCS; Toshiyuki Nishikido, PhD; Lawrence A. Leiter, MD; Ulf Landmesser, PhD; R. Scott Wright, MD; Peter L. J. Wijngaard, PhD; John J. P. Kastelein, PhD

Figure 3. Persistence of Response

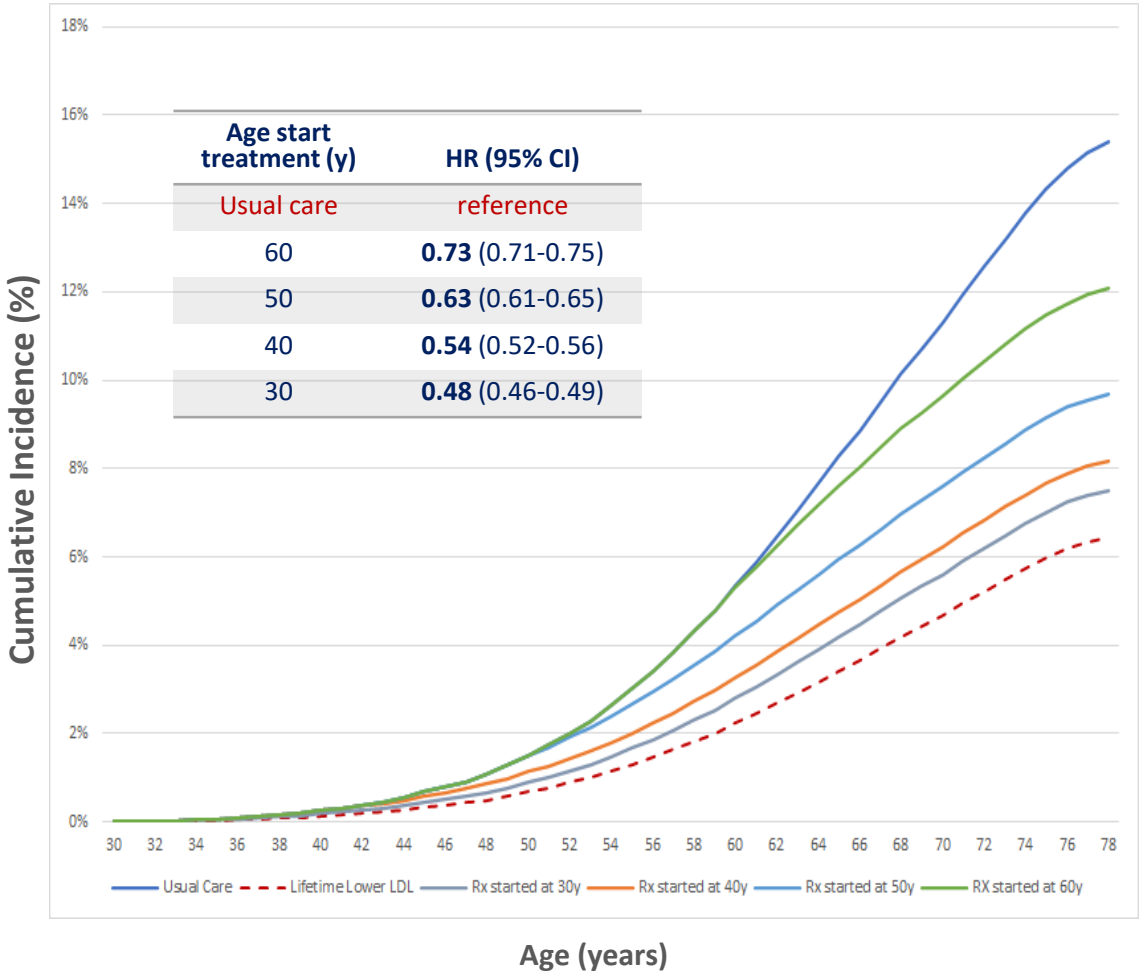


Defined as days taken for individuals to return to within 20% of their change from baseline low-density lipoprotein cholesterol levels up to day 360.

Estimating benefit of lowering LDL by inhibiting PCSK9 with once yearly dose of siRNA

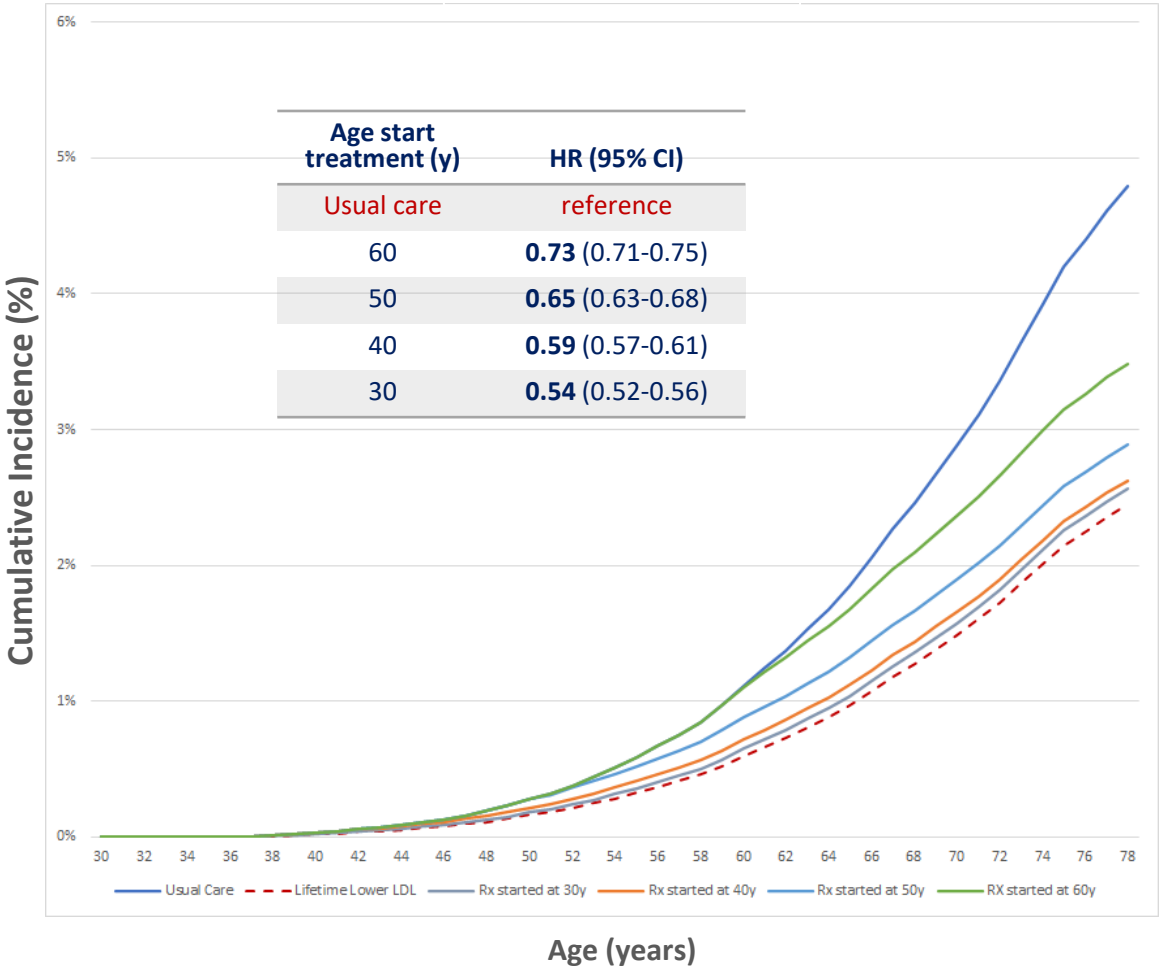
Men

Age start treatment (y)	HR (95% CI)
Usual care	reference
60	**0.73** (0.71-0.75)
50	**0.63** (0.61-0.65)
40	**0.54** (0.52-0.56)
30	**0.48** (0.46-0.49)



Women

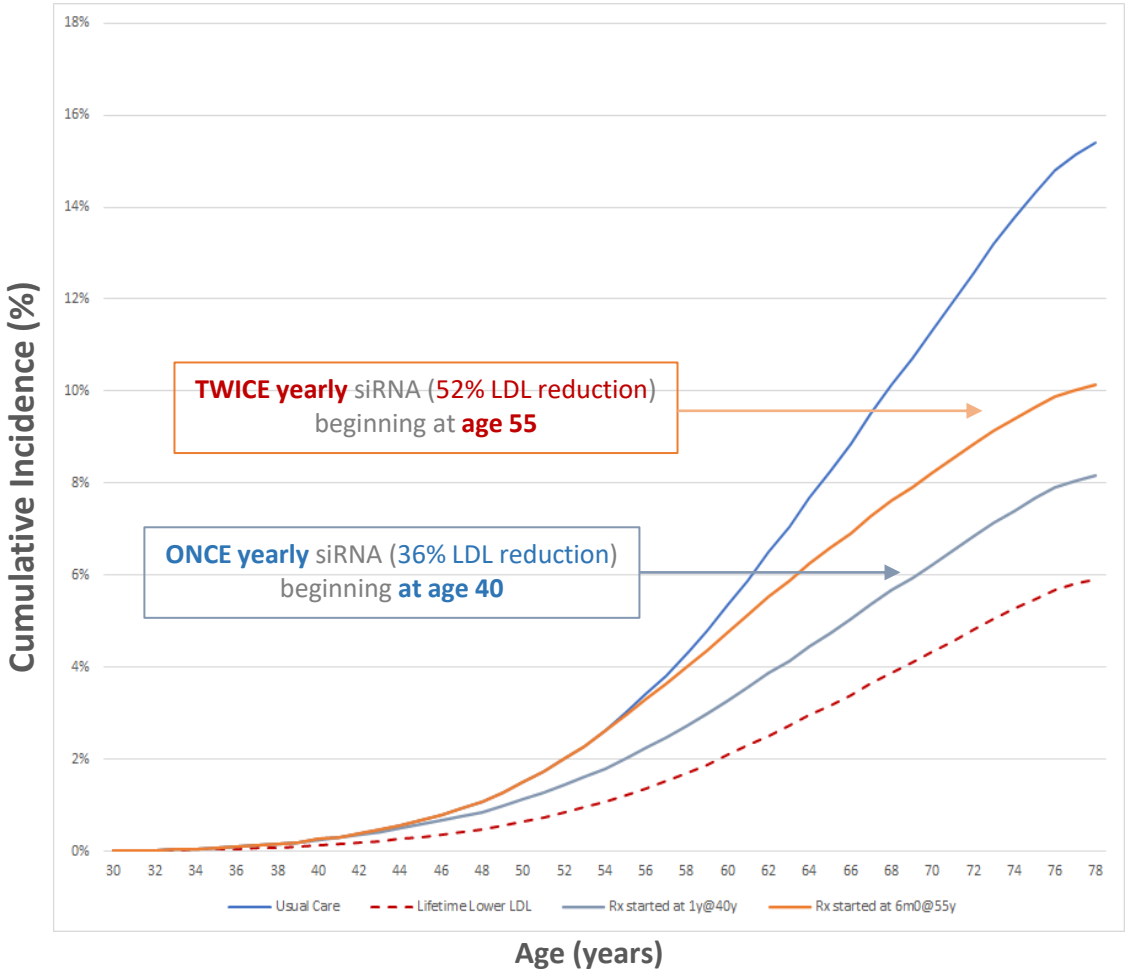
Age start treatment (y)	HR (95% CI)
Usual care	reference
60	**0.73** (0.71-0.75)
50	**0.65** (0.63-0.68)
40	**0.59** (0.57-0.61)
30	**0.54** (0.52-0.56)



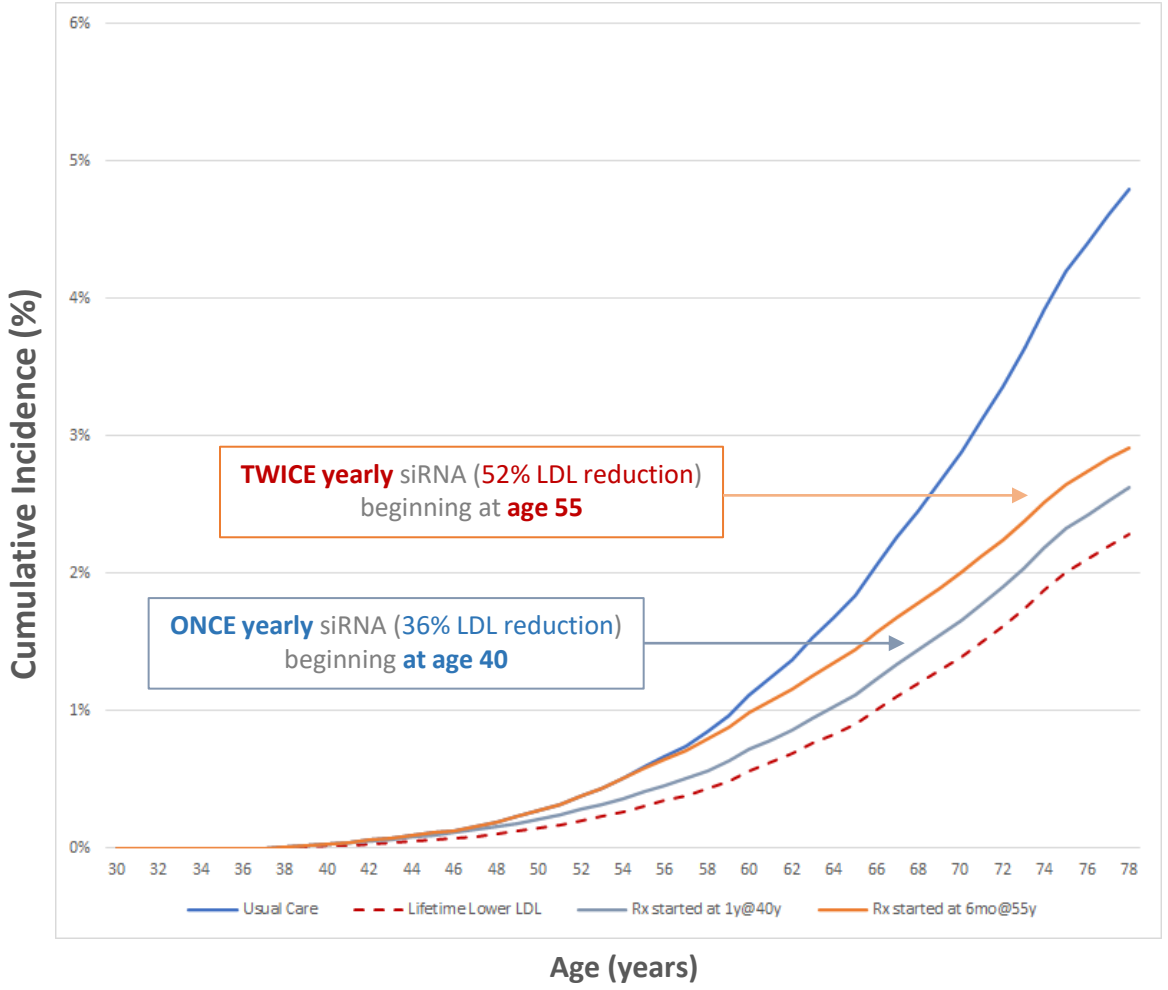
Ference BA , …..Ray KK ESC 2021 Late Breaking Science

Comparing once yearly PCSK9 siRNA started earlier with twice yearly doses started later

Men



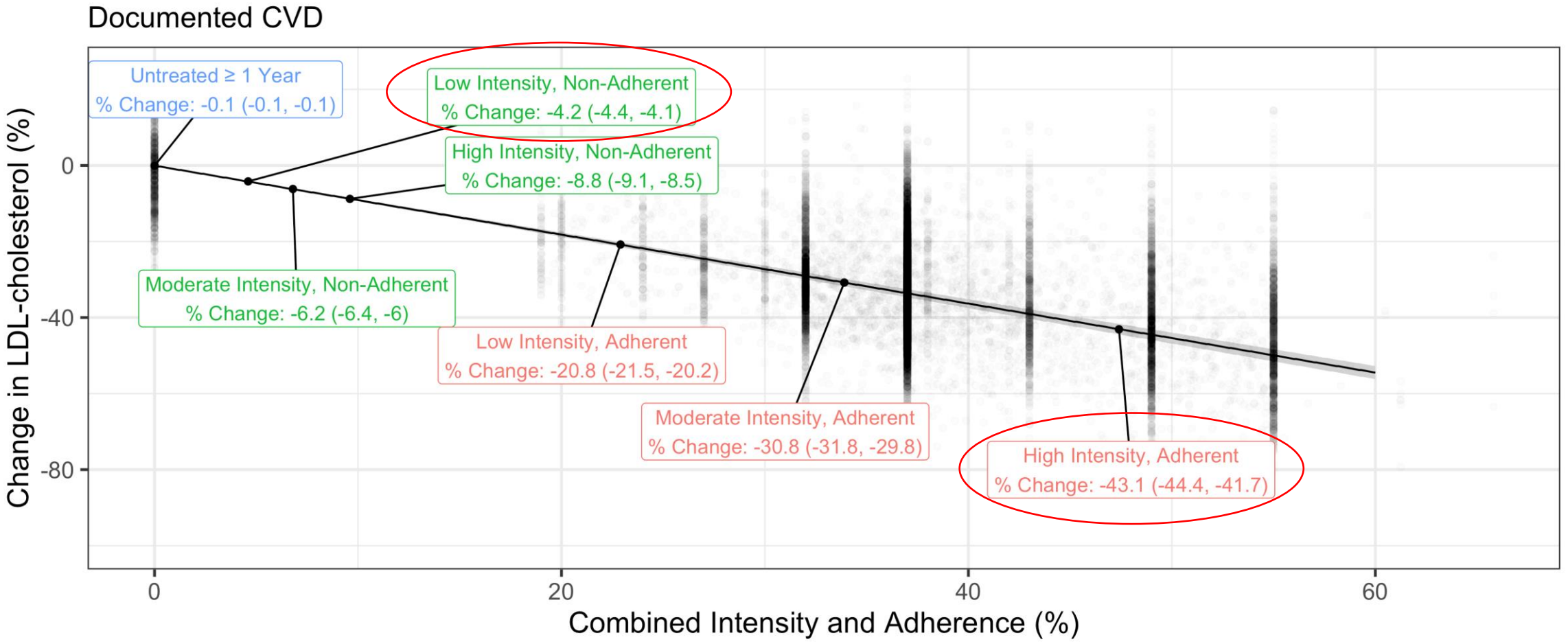
Women



Ference BA , …..Ray KK ESC 2021 Late Breaking Science

LDL-C long-term exposure with small molecules- the challenge of doctor patient behavior:

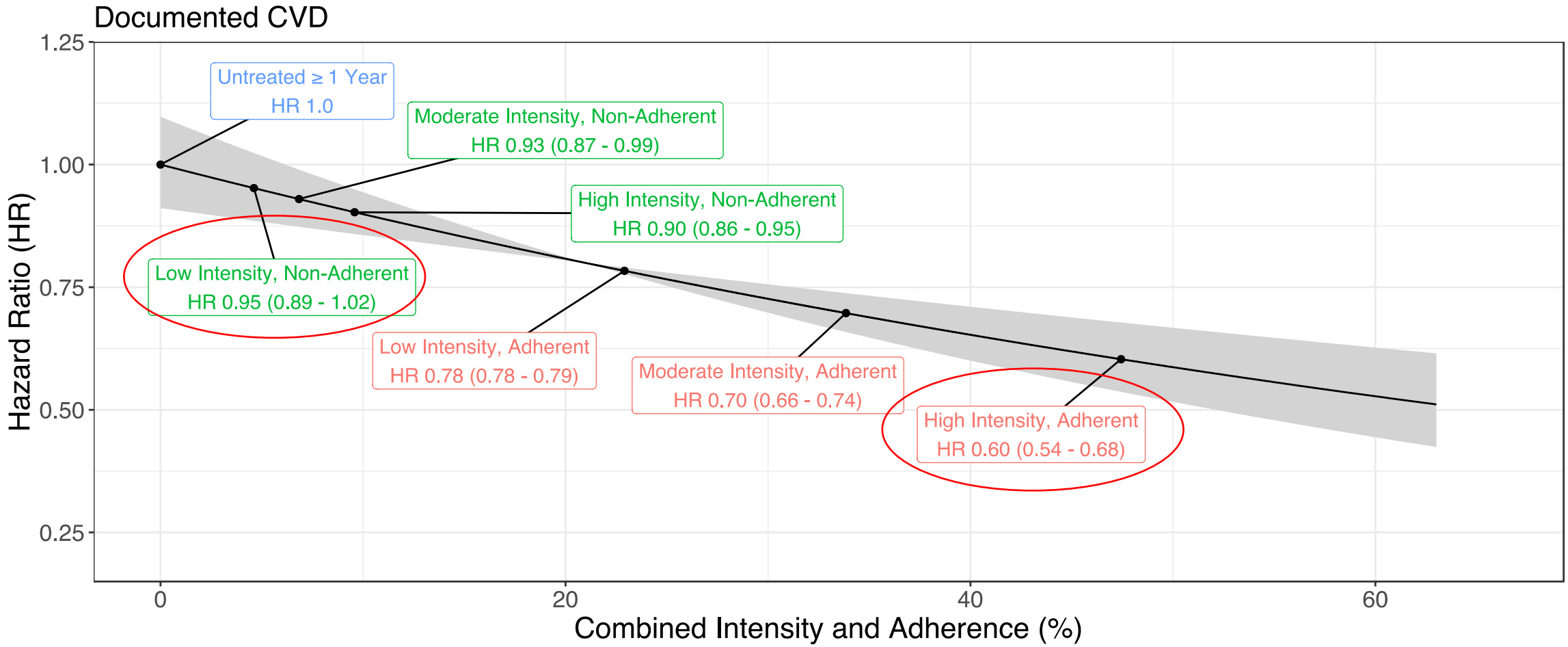
Combined Measure of Adherence x Intensity on LDL-C Reduction



Results for diabetes and CKD cohorts were similar

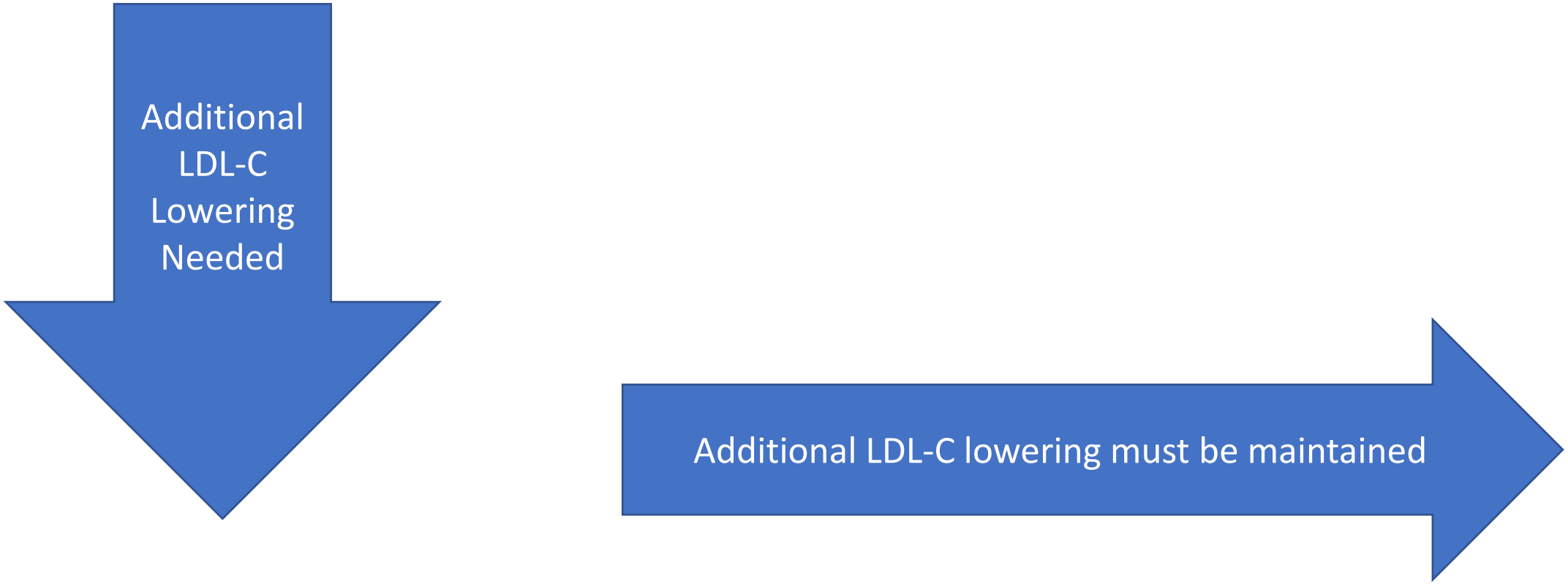
Khunti K , Ray KK JAMA Network Open Dec 7th 2018 1(8):e185554. doi:10.1001/jamanetworkopen.2018.5554

Adherence to daily dosing regimens remains a challenge and poor adherence is associated with adverse outcomes



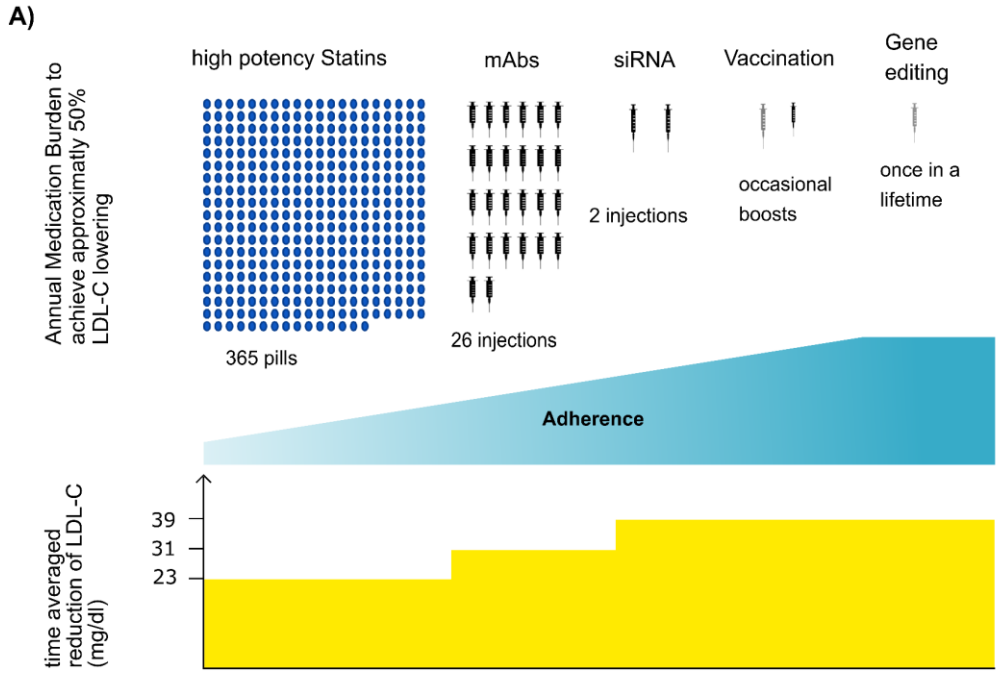
Khunti K , Ray KK JAMA Network Open Dec 7th 2018 1(8):e185554. doi:10.1001/jamanetworkopen.2018.5554

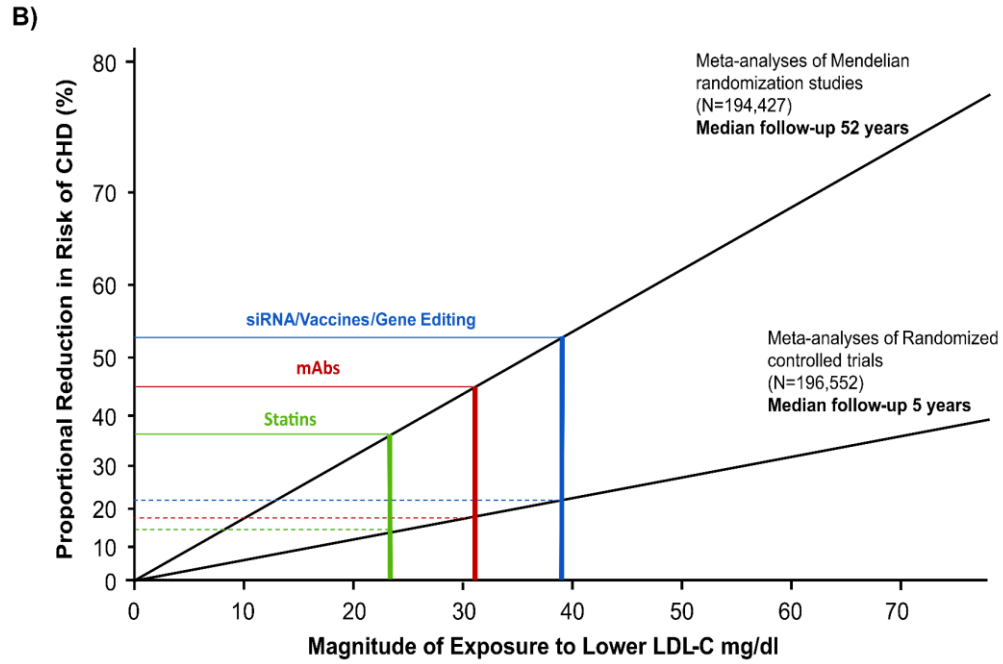
Monotherapy is unlikely to reach very low LDL-C goals for most?



Tackling Cholesterol Together

Moving to a cumulative Exposure Model for Population Health





Brandts J, Ray KK Circulation 2020

Have we reached the limits of CVD risk reduction?

No

We're just getting started

Real World clinical experience

- Male 64 Greek – First non-trial UK patient
- 25 years of statins-increased intensity of statins then ezetimibe
- Probable HeFH moderate atheroma on CT angio
- LDL-C 3.4 mmol/L

- Single inclisiran 30 days later
- LDL-C 1.6mmol/L

- 54 male ASCVD
- LDL-C 1.6 on statins Lp(a) high

- Evolocumab LDL-C 0.6mmol/L

- Switch to Inclisiran
- LDL-C 30 days later
- 0.7mmol/L

- Polygenic hypercholesterolaemia

- Primary prevention
- Statin and ezetimibe intolerance
- LDL-C 5.4 mmol/L

- Injection Inclisiran
- LDL-C 2.6mmol/L

Conclusion

- There is a considerable burden of CVD
- Improving control of LDL-C can significantly reduce that
- In part this is due to poor adherence with small molecules and the low likelihood of monotherapy achieving very low LDL-C goals
- Combination of statins which increase LDL-R and therapies that lower PCSK9 can increase the survival of those receptors
- New injectable RNA based therapies could improve population health

05 Q&A

Next steps:

Join us and book for the next webinars:

Weds 19th Jan 2022 1-2pm (time tbc)

Statin hesitancy, health investment and benefits over time:
Dr Derek Connolly, Professor Terry McCormack and Professor Handrean Soran will discuss statin hesitancy, suspected statin intolerance and how to frame lipid lowering therapy as a long-term health investment.

Weds 16th Feb 2022 1-2pm

Diabetes, obesity & lipids:
Dr Derek Connolly, Professor Terry McCormack, Dr Jim Moore and Dr Adie Viljoen will review multiple mechanisms of how diabetes and obesity increases cardiovascular risk, the metabolic syndrome, and the subsequent increased risk for acute coronary events.

Keep an eye out on the TCT home pages on the HEART UK website for the informal case based interactive clinics

All programme content, recordings and next webinar bookings will be housed in the HEART UK pages. Visit the site for the new e-Learning modules on Identifying FH in primary care, Statin Intolerance, and the Lipid Management Pathway

Lowering Cholesterol.

Saving Lives.

TheAHSNNetwork

ACCELERATED ACCESS COLLABORATIVE

HEART UK THE CHOLESTEROL CHARITY

NHS

Tackling Cholesterol Together

Thank you

This webinar has now finished.

Today's slides and recording will be available after the webinar on the HEART UK pages. Visit the site for the **new** e-Learning modules on diet launching in November. Identifying FH in primary care, Statin Intolerance, and the Lipid Management Pathway modules are also available.

All programme content, recordings and next webinar bookings will be housed here: https://www.heartuk.org.uk/tackling-cholesterol-together/home