Lowering Cholesterol.

Saving Lives.

TheAHSNNetwork

ACCELERATED ACCESS COLLABORATIVE

HEART UK THE CHOLESTEROL CHARITY

NHS

Tackling Cholesterol Together

Evaluating Cardiovascular Disease Risk

Welcome to the first 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 1pm

July 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

The NHS Accelerated Access Collaborative (AAC) and The AHSN Network are partnering with the cholesterol charity, HEART UK, to build a new national education programme called Tackling Cholesterol Together.

Launches July 2021 and available through the HEART UK pages https://www.heartuk.org.uk/tackling-cholesterol-together/home.

Free to access, **broad range** of digital learning tools

Supports healthcare professionals in primary and secondary care to **take control** of cholesterol management

Enables professionals to discover methods to **rectify** under diagnosis and under treatment at scale

Finds ways to use **new models** to address the real-world challenges of cholesterol management

Supports the Long Term Plan's ambitions and will **boost** uptake of proven cholesterol-lowering drugs

In line with updated NICE endorsed clinical pathways, including **new** recommended therapies

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
- **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 and Introductions**	Christopher Allen
02	**CVD and Lipid Management in England Today**	Dr Shahed Ahmad
03	**Evaluating Cardiovascular Disease Risk**	Dr Peter Green
04	**Beyond risk scores - risk in Familial Hypercholesterolaemia (FH) and established atherosclerotic cardiovascular disease (and what to do about it)**	Dr Dermot Neely
05	**Close and next steps**	Christopher Allen

Objectives of today's Webinar

01

Understand effective lipid management for patients in the context of national priorities for the NHS in England in the prevention and management of CVD

02

Gain **knowledge** of the NICE guidance on CVD risk assessment tools, how to interpret risk

03

Gain **insight** into the role of cholesterol as a modifiable CVD risk factor

04

Develop methods to evaluate and manage risk when risk scores are not recommended

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02

CVD and Lipid Management in England Today

Dr Shahed Ahmad

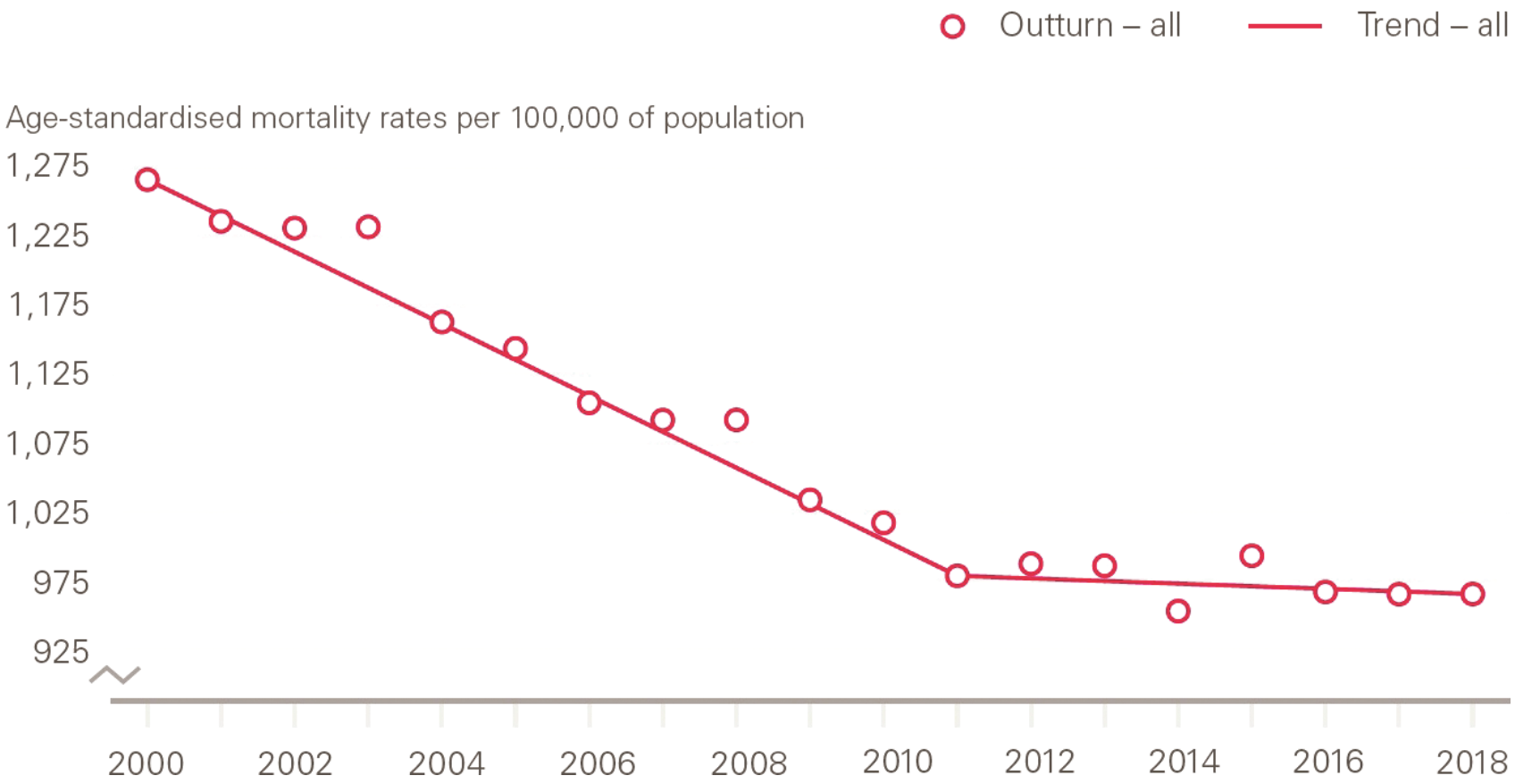
National Clinical Director for Cardiovascular Disease Prevention at NHS England and Improvement

We will cover:

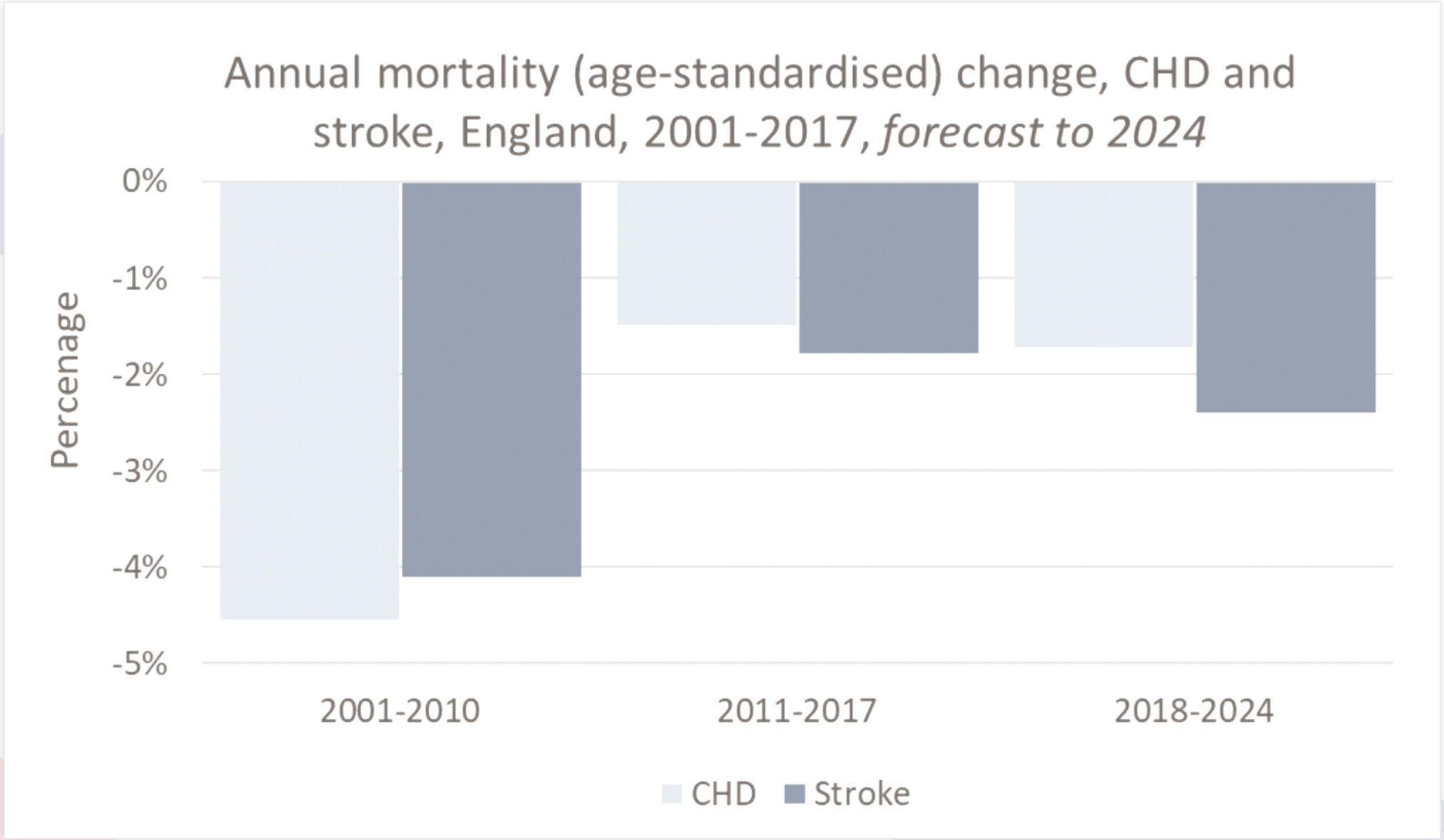
- Why CVD is a priority
- CVD and health inequalities
- LTP national ambitions for CVD prevention in the NHS in England

Why is CVD a priority?

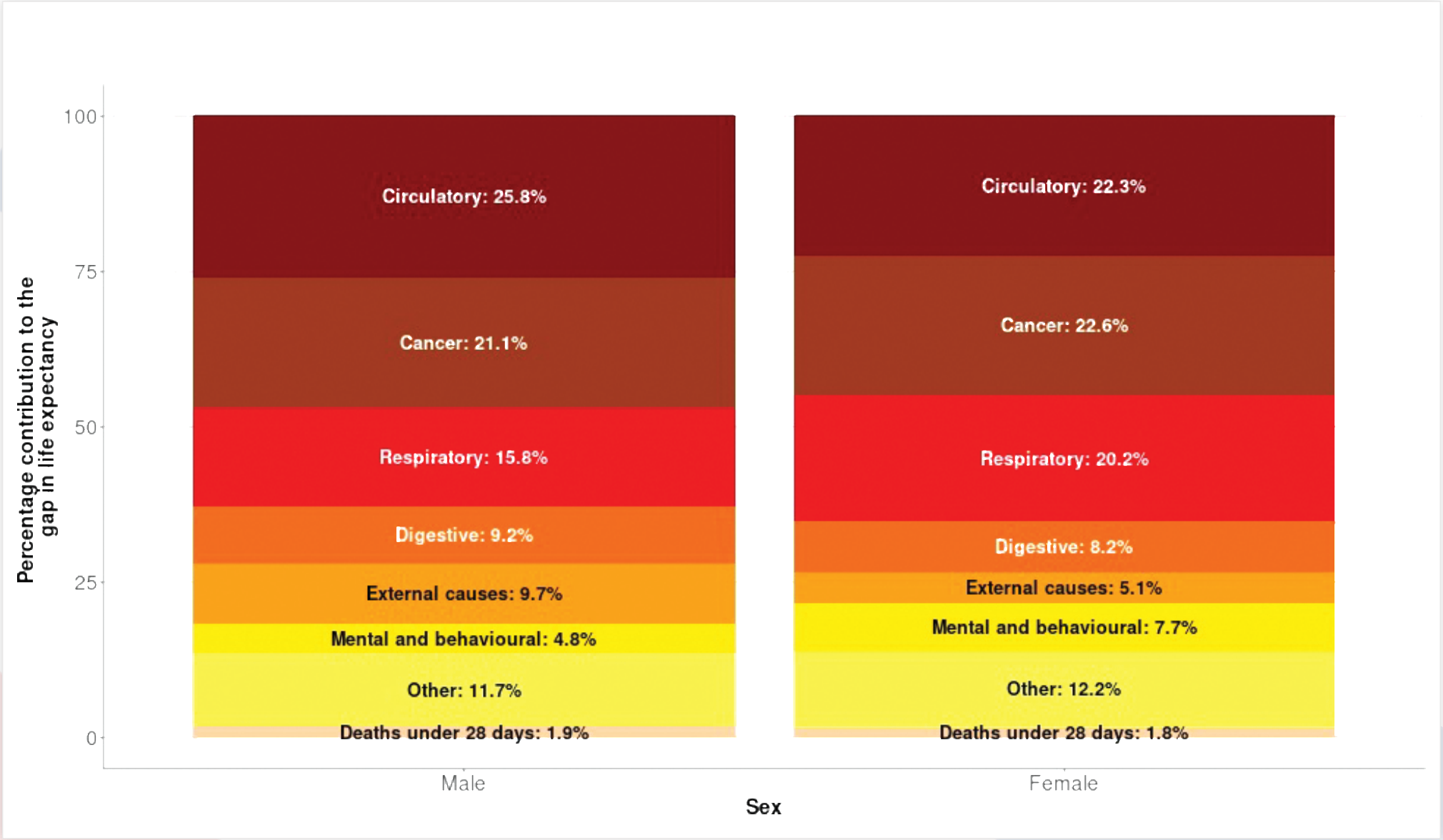
Figure 6: The changed trend in mortality rate improvements: England and Wales, 2000–2018



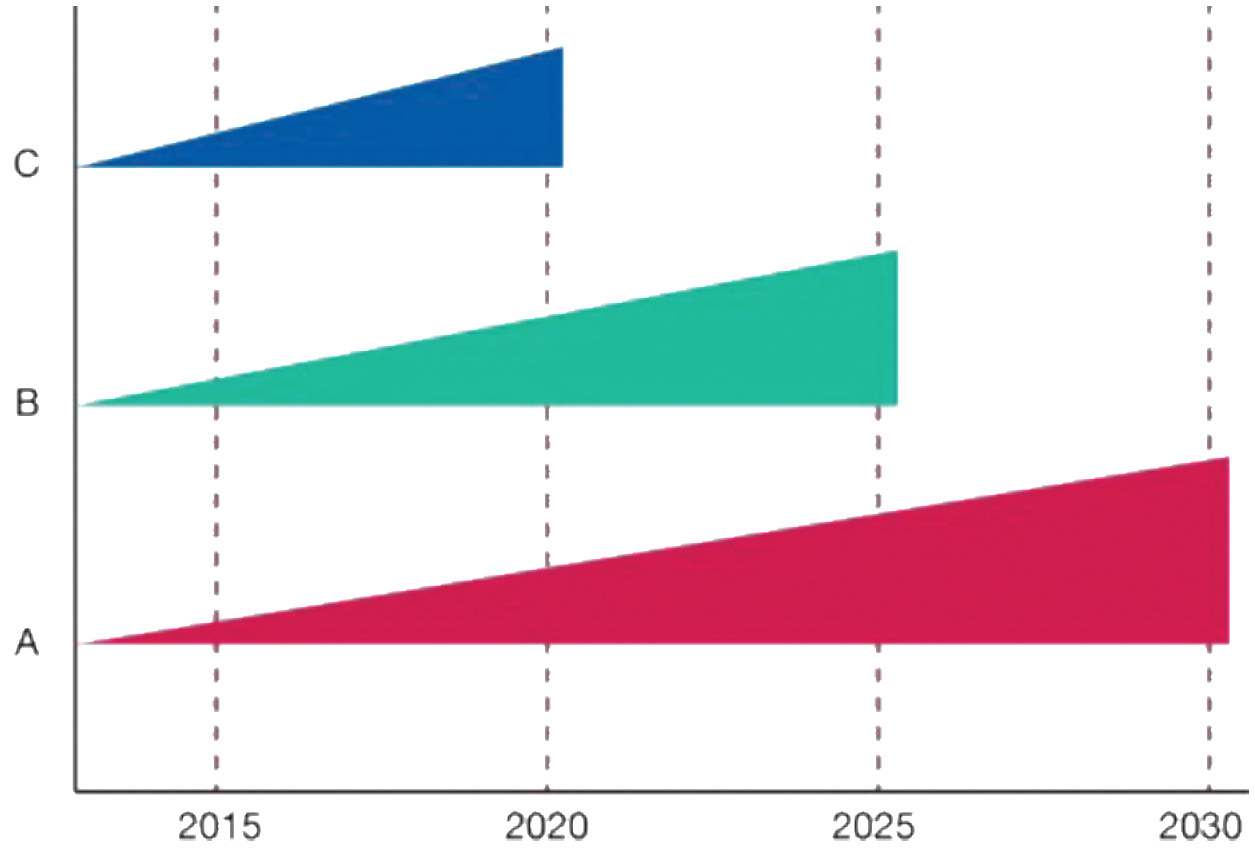
Why is CVD a priority?



Why is CVD a priority?



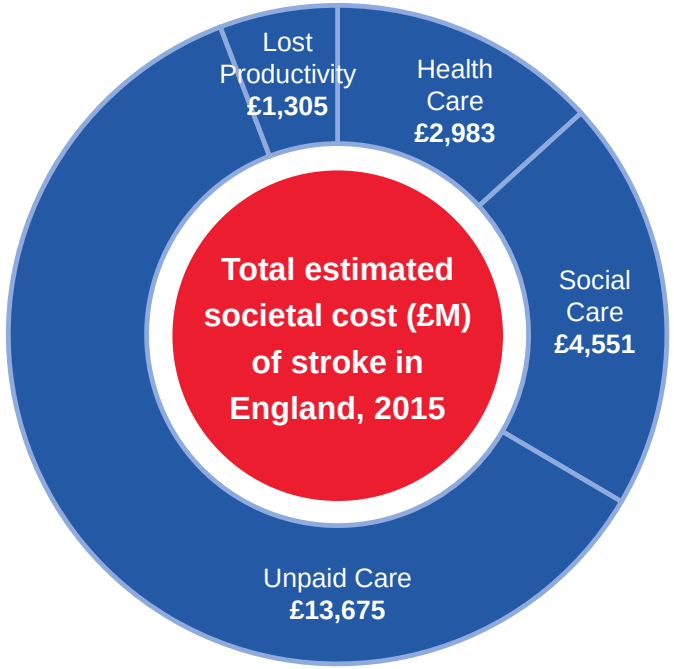
Why is CVD a priority?



Why is CVD a priority?

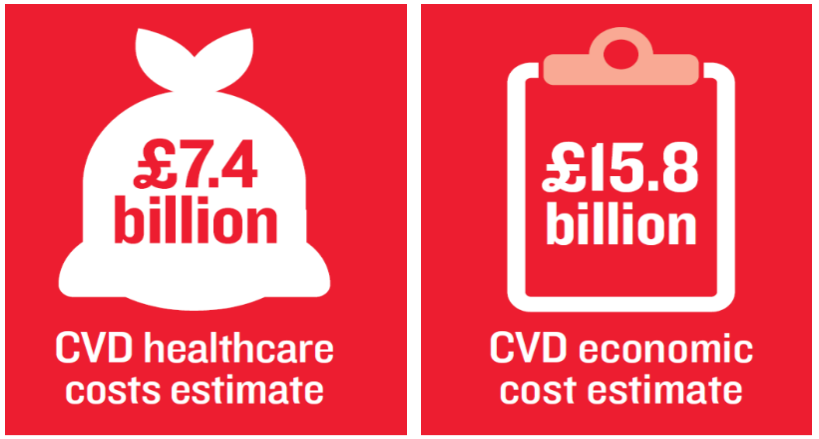
- **CVD kills 136,000 people a year**
- CVD differentially targets **ethnic minority communities**
- CVD differentially targets **deprived communities**
- As well as death, CVD can cause **significant disability**
- **CVD can be prevented**

STROKE IS THE LARGEST CAUSE OF ADULT DISABILITY



Source: Stroke Association. Current, future and avoidable costs of stroke

CVD IS EXPENSIVE



Source: BHF analysis of European Heart Network (2017)
European Cardiovascular Disease Statistics 2017

Cardiovascular disease: A major cause of health inequalities

- **CVD remains the leading cause** of premature mortality in England, and the rate of improvement seen in recent years has slowed
- **It is also one of the conditions** most strongly associated with health inequalities, with people living in England's most deprived areas being almost four times more likely to die prematurely of CVD than those in the least deprived areas
- **As well as living shorter lives on average**, people in more deprived areas are affected by a range of conditions that significantly impact on their quality of life
- **For example**, those in the most deprived communities are 30% more likely to have high blood pressure, which is the largest single risk factor for heart attack and stroke

NHS Long Term Plan

- The NHS Long Term Plan provides a platform to transform the way we tackle CVD in England and pledges a rejuvenated call to address CVD inequalities
- Prevention is at the heart of the NHS Long Term Plan
- The plan includes a major ambition to **prevent 150,000 heart attacks, strokes and dementia cases over the next 10 years** by improving the treatment of high-risk conditions – **hypertension, high cholesterol and atrial fibrillation**, which leave patients a greater risk of developing CVD

Transforming CVD and lipid management as a national agenda

The NHS Long Term Plan states that the biggest area where the NHS can save lives over the next 10 years is in reducing the incidence of CVD
CVD causes a quarter of all deaths in the UK and is the largest cause of premature mortality in deprived areas

To help tackle the challenges with CVD management and to support the Long Term Plan ambition, NHS England Improvement have commissioned a national primary care audit – $CVD_{PREVENT}$

CVD prevention ambitions: Cholesterol

Assessment

By **2029, 75%** of eligible people aged **40** to **74** without established CVD (such as a previous heart attack or stroke), have a validated CVD risk assessment and cholesterol reading recorded on a primary care data system in the last **5** years.

Treatment

By **2029, 45%** of people aged **40** to **74** without established CVD who are identified as having a **20%** or greater **10**-year risk of developing CVD in primary care are treated with statins.

Diagnosis

By **2024**, **25%** of people with familial hypercholesterolaemia are diagnosed and treated in line with the NICE guideline on familial hypercholesterolaemia.

Source: PHE health matters preventing cardiovascular disease 2019

03

Evaluating Cardiovascular Disease Risk

Dr Peter Green

Clinical lead for CVD Prevent, NHS England and NHS Improvement, Chair HEART UK, practising GP

We will cover:

NICE recommendations and screening tools

Factors that contribute to CVD risk

The benefit of lipid lowering therapy in primary prevention of CVD

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

Why Do We Need to Find Patients at Risk of CVD?

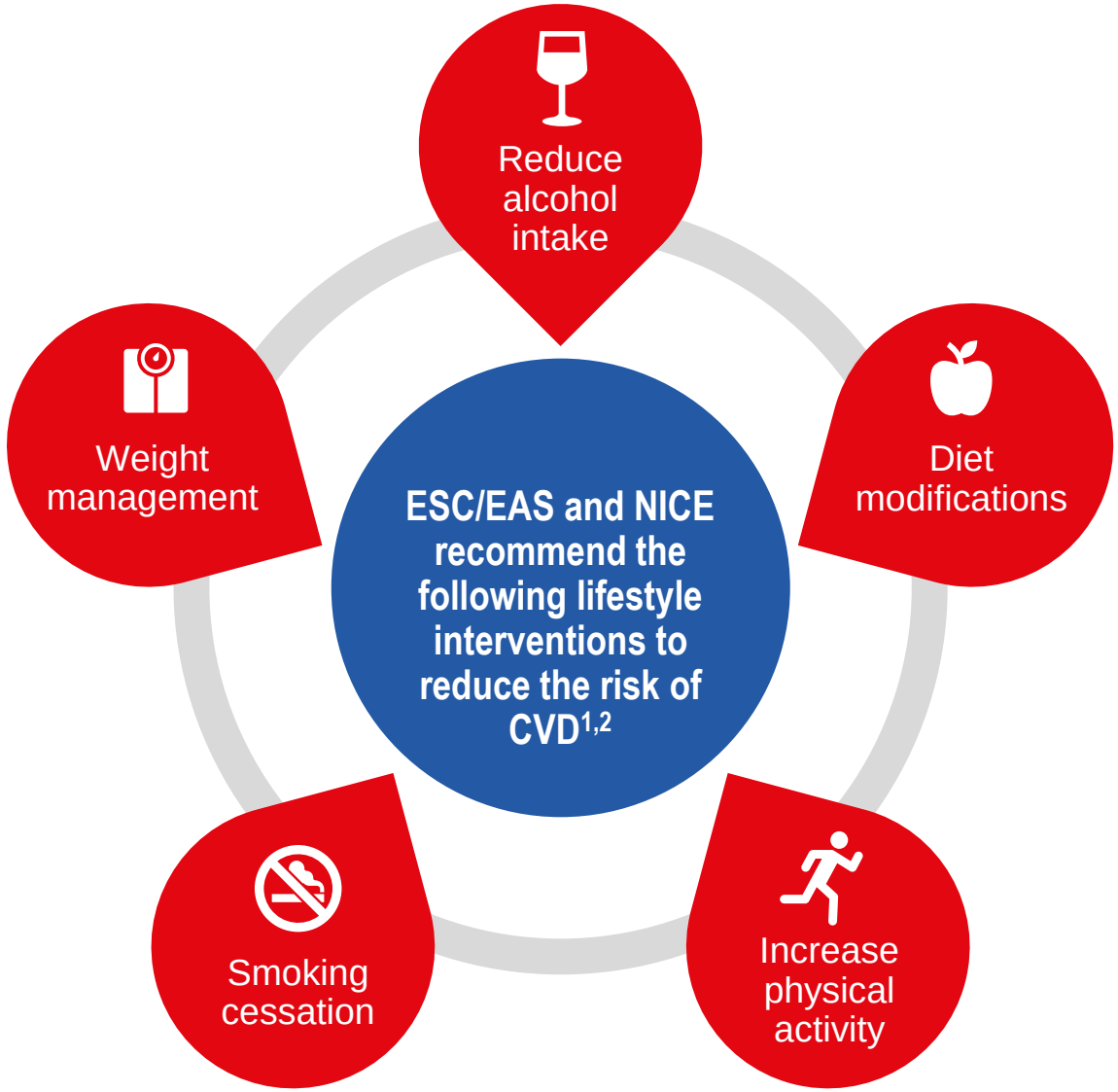
~80% Almost 80% of patients on Lipid Lowering Therapies failed to reach an LDL-C goal of <1.8 mmol/L[1]

~1:250 Incidence of heterozygous FH;[2] only 12% of cases are identified in the UK[3]

Aggressive LDL-C targets[4] are based on evidence showing significant CV outcomes benefits[5–9]

Therefore, screening for patients with high-risk CVD and FH is a critical part of primary care

Lifestyle Changes Are Recommended for Patients at High-Risk of CVD



Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD

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INITIAL CONSIDERATIONS:

● Measure non-fasting **full lipid profile** (Total cholesterol, HDL-C, non-HDL-C, triglycerides) and HbA1c as part of an initial baseline assessment. ● Consider secondary causes of hyperlipidaemia and manage as needed. ● Ensure appropriate baseline and follow up tests as detailed on page 2. Measure BMI. ● Identify and exclude people with contraindications/drug interactions ● If non-fasting triglyceride above 4.5mmol/L see page 2.

PRIMARY PREVENTION

Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2, 'Primary Prevention Risk Assessment')

- Age ≤84 & QRISK ≥10% over next 10 years
- Type 2 diabetes & QRISK ≥10% over next 10 years
- Type 1 diabetes, if they have one or more of the following:
  - Over 40 years
  - Had diabetes for >10 years
  - Have established nephropathy
  - Have other CVD risk factors
- CKD eGFR < 60 mL/min/1.73m2 and/or albuminuria
- Age ≥85 yearsif appropriate consider comorbidities, frailty & life expectancy

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors).

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate offer statin treatment.
Atorvastatin 20mg OD

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months;
  - Discuss treatment adherence, timing of dose, diet and lifestyle
  - If at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 'Additional Risk Factors') consider increasing the dose every 2-3 months up to a maximum dose of atorvastatin 80mg OD.
  - For how to increase in people with CKD see 'Special Patient Populations' (page 2)

- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 'Statin Intensity Table')
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value after 3 months consider adding Ezetimibe 10mg OD (NICE TA385)
- If recommended statin therapy is contraindicated or not tolerated;
  - Ezetimibe monotherapy may be considered. Assess response after 3 months
  - See local statin intolerance guidance / pathway where available

If non-HDL-C reduction remains < 40% of baseline despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications) consider referral to specialist lipid management clinic according to local arrangements.

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, a personal and/or family history of confirmed CHD (<60 years) and no secondary causes: suspect Familial Hypercholesterolaemia (Possible Heterozygous FH)
Do not use QRISK risk assessment tool

DIAGNOSIS AND REFERRAL

Take fasting blood for repeat lipid profile to measure LDL-C.
Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH.
Refer to Lipid Clinic for further assessment if clinical diagnosis of FH
or if TC>9.0mmol/L and/or
LDL-C >6.5mmol/L and/or
non-HDL-C >7.5mmol/L or
Fasting triglycerides > 10mmol/L
(regardless of family history) (page 2)

TREATMENT TARGETS IN FH

If clinical diagnosis of FH and/or other risk factors present, follow the recommended treatment management pathway for primary or secondary prevention as for non-FH, BUT
Aim to achieve at least a 50% reduction of LDL-C (or non-fasting non-HDL-C) from baseline.
Consider specialist referral for further treatment and/or consideration of PCSK9i therapy IF
- they are assessed to be at very high risk of a coronary event**
- OR therapy is not tolerated
- OR LDL-C remains >5mmol/L (primary prevention)
- OR LDL-C remains >3.5mmol/L (secondary prevention)

Despite maximal tolerated statin and Ezetimibe therapy.
**defined as any of the following:
- Established coronary heart disease.
- Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes angina, previous MI, revascularisation, stroke or TIA or symptomatic peripheral arterial disease. Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours)

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors.
Prescibe a high intensity statin:
Atorvastatin 80mg OD
Use a lower dose of Atorvastatin if there is a potential drug interaction, high risk of or experiencing adverse effects, or patient preference.
Offer Atorvastatin 20mg if CKD (people with GFR< 60 mL/min/1.73m2).

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months
  - Discuss treatment adherence, timing of dose, diet and lifestyle measures
  - If started on less than atorvastatin 80mg and the person is judged to be at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 'Additional Risk Factors'), consider increasing to 80mg Atorvastatin. For how to increase in people with CKD see 'Special Patient Populations' (page 2).
- If non-HDL-C baseline value is not available, use target non-HDL-C < 2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/L) as recommended by JBS3 consensus statement - a **'lower is better approach'**
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 'Statin Intensity Table')

- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value and/or non-HDL-C < 2.5mmol/L after 3 months consider adding Ezetimibe 10mg OD **(NICE TA385)**
- If recommended statin therapy is contraindicated or not tolerated
  - Ezetimibe monotherapy may be considered. Assess response after 3 months
  - See local statin intolerance guidance/pathway where available.

If non-HDL-C > 4.0mmol/L despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications), arrange a **fasting blood test** for LDL-C measurement and if **PCSK9i eligibility criteria** (see page 2 'Specialist Services') are met, refer for confirmation and initiation of PCSK9i (NICE TA 393, 394) according to local arrangements.

Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD

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PRIMARY PREVENTION

Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2, 'Primary Prevention Risk')

Age ≤84 & QRISK ≥10% over next 10 years	Type 2 diabetes & QRISK ≥10% over next 10 years	Type 1 diabetes, if they have one or more of the following: • Over 40 years • Had diabetes for >10 years • Have established nephropathy • Have other CVD risk factors	CKD eGFR < 60 mL/min/1.73m2 and/or albuminuria	Age ≥85 years if appropriate consider comorbidities, frailty & life expectancy

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors)

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

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

WOSCOPS: Investigation Into the Long-term Impact of LDL-C Lowering on CV Outcomes in Men With Hypercholesterolaemia

Study design and objectives

6,595 men

KEY INCLUSION CRITERIA

- 45–65 years
- LDL-C ≥4.0 mmol/L (155 mg/dL) and ≥4.5 mmol/L (174 mg/dL) on two separate fasting lipid measurements
- No prior MI
- Not receiving LLT

KEY EXCLUSION CRITERIA

- LDL-C ≥6.0 mmol/L (232 mg/dL) on two fasting lipid measurements†

Pravastatin 40 mg/day

Placebo

Average follow up: 4.9 years

PRIMARY OUTCOME: Composite of death from CHD and nonfatal MI as a first event*

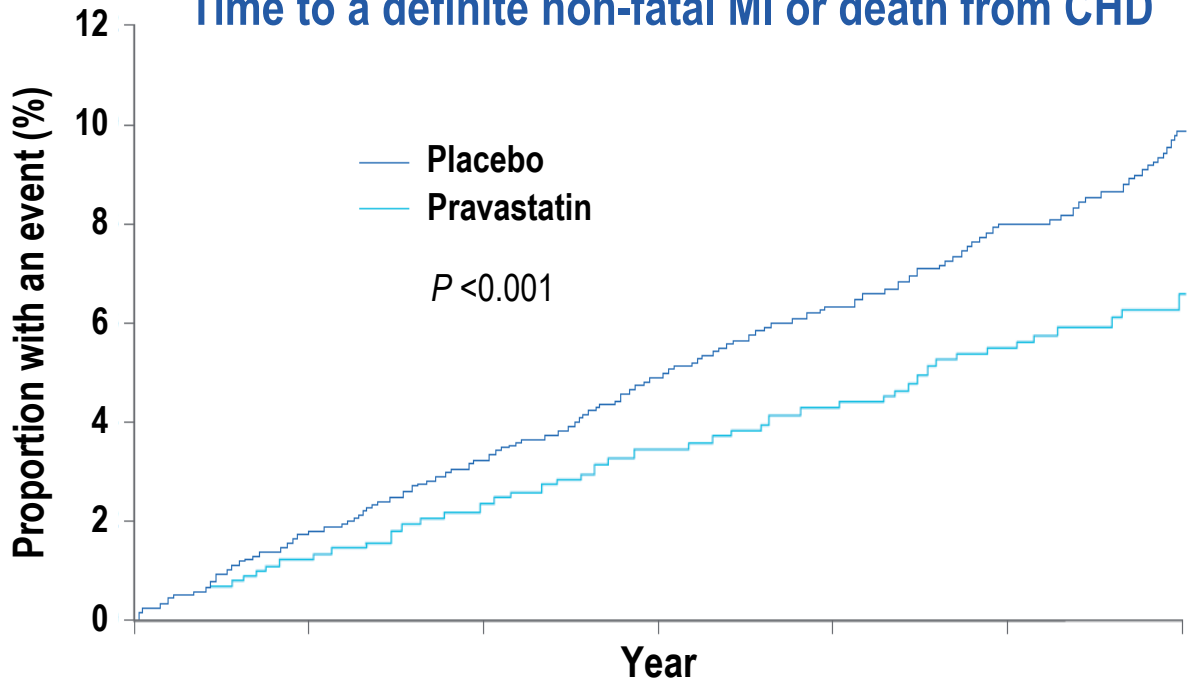
*Determined from medical records, electrocardiographic recordings and the national death registry.
†Between visits 2 and 4 before randomisation.
CHD, coronary heart disease; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; WOSCOPS, The West of Scotland Coronary Prevention Study.
Shepherd, et al. N Engl J Med. 1995;333:1301–1307.

WOSCOPS: Primary CVD Prevention With Pravastatin Reduced the Risk of Fatal CHD and Nonfatal MI Compared With Placebo

Initial results

- Pravastatin lowered plasma TC and LDL-C levels by 20% and 26% from baseline, respectively;
  there were no changes with placebo*
- Compared with placebo, non-fatal MI or death from CHD with pravastatin was associated with:
  - ARR: 2.4%
  - RRR: 31% (95% CI: 17–43%; *P* <0.001)
- No significant difference between the two groups in:
  - Incidence of cancers (fatal or non-fatal)
  - Incidence of myalgia
  - ALT and AST elevations

Time to a definite non-fatal MI or death from CHD



	0	1	2	3	4	5	6
Placebo cumulative events	0	55	105	159	205	240	248
No. at risk	3293	3230	3167	3099	2714	1241	83
Pravastatin cumulative events	0	40	72	109	138	167	174
No. at risk	3302	3256	3215	3162	2807	1330	99

*On-treatment analysis.

ALT, alanine aminotransferase; ARR, absolute risk reduction; AST, aspartate aminotransferase; CHD, coronary heart disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; RRR, relative risk reduction; TC, total cholesterol; WOSCOPS, The West of Scotland Coronary Prevention Study.

Shepherd, et al. N Engl J Med. 1995;333:1301–1307.

WOSCOPS: The risk reduction from 5 years of pravastatin therapy was persistent

20 year follow up

- All cause mortality rate:38% placebo group 34.7% statin group
- Cardiovascular and CHD mortality rates were also reduced
- Mortality from stroke, non-cardiovascular causes and cancer did not change significantly.
- The risk reduction in cardiovascular outcomes from 5 years of pravastatin therapy was persistent over the 20-year period and led to reduced mortality and hospitalizations

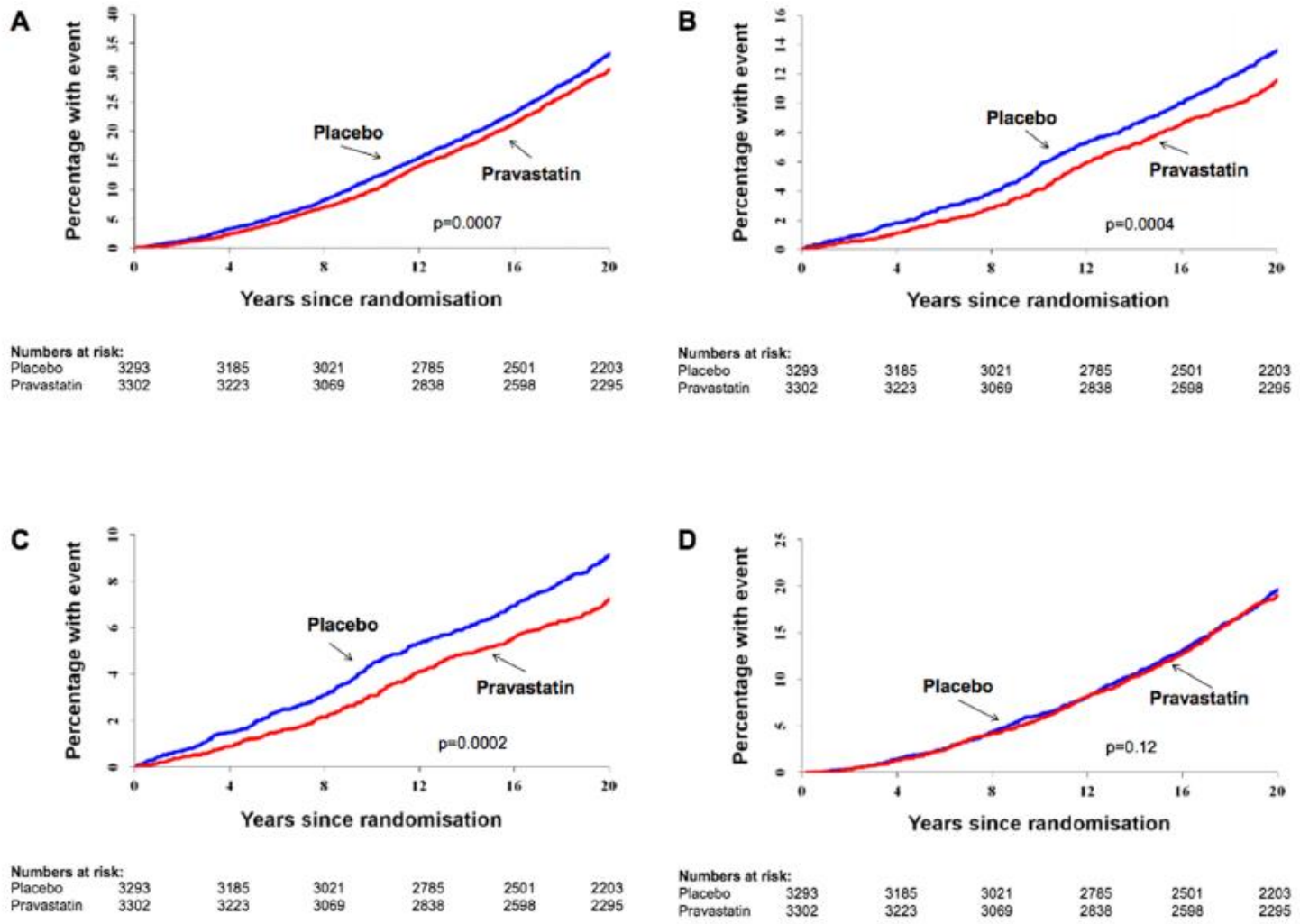
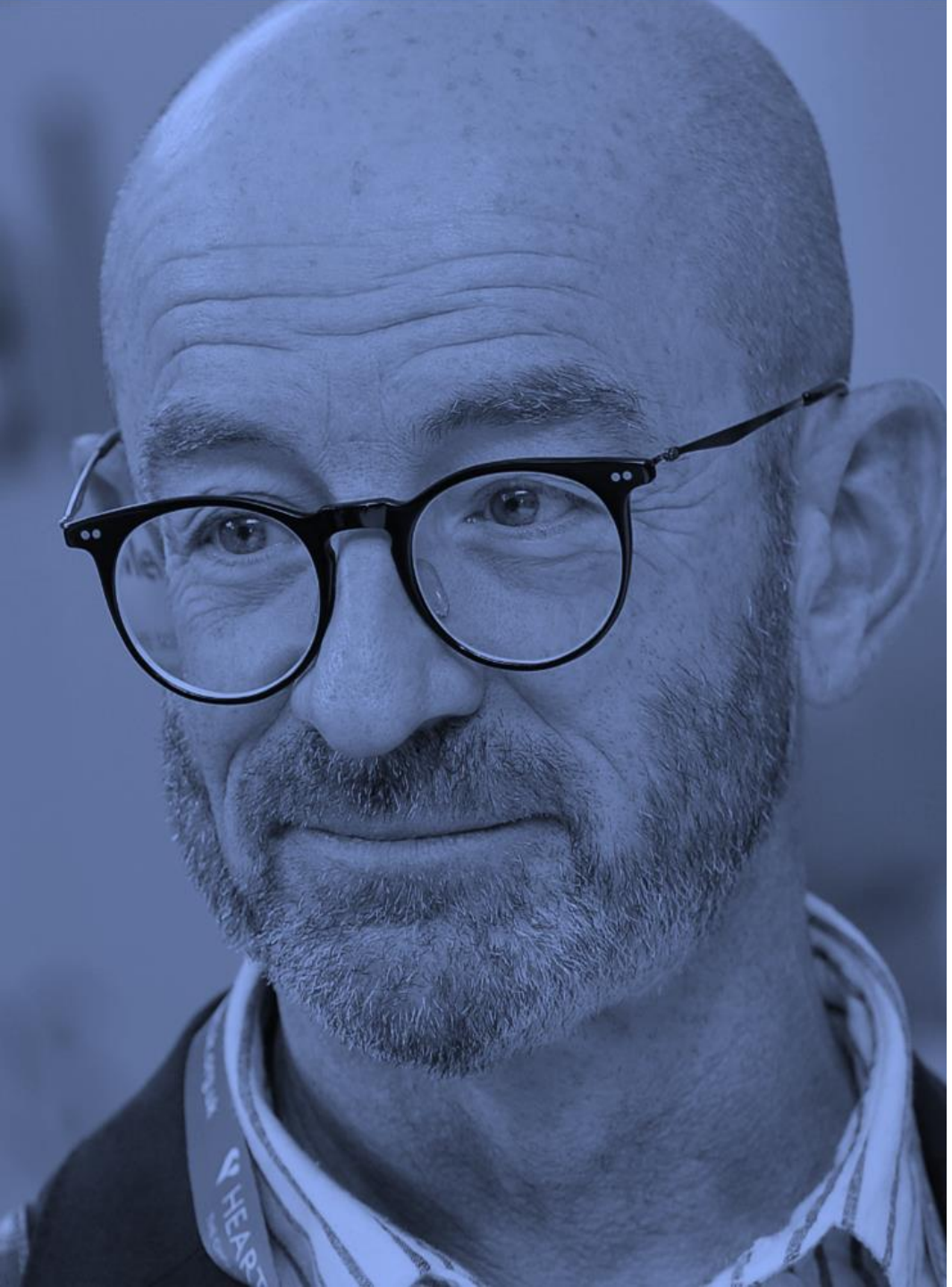


Figure 1. Cumulative mortality from (A) all causes, (B) cardiovascular disease, (C) coronary heart disease, and (D) non-cardiovascular disease. *P* values were determined by Cox proportional hazards model.[7]



04

Beyond risk scores - risk in Familial Hypercholesterolaemia and established atherosclerotic cardiovascular disease (and what to do about it)

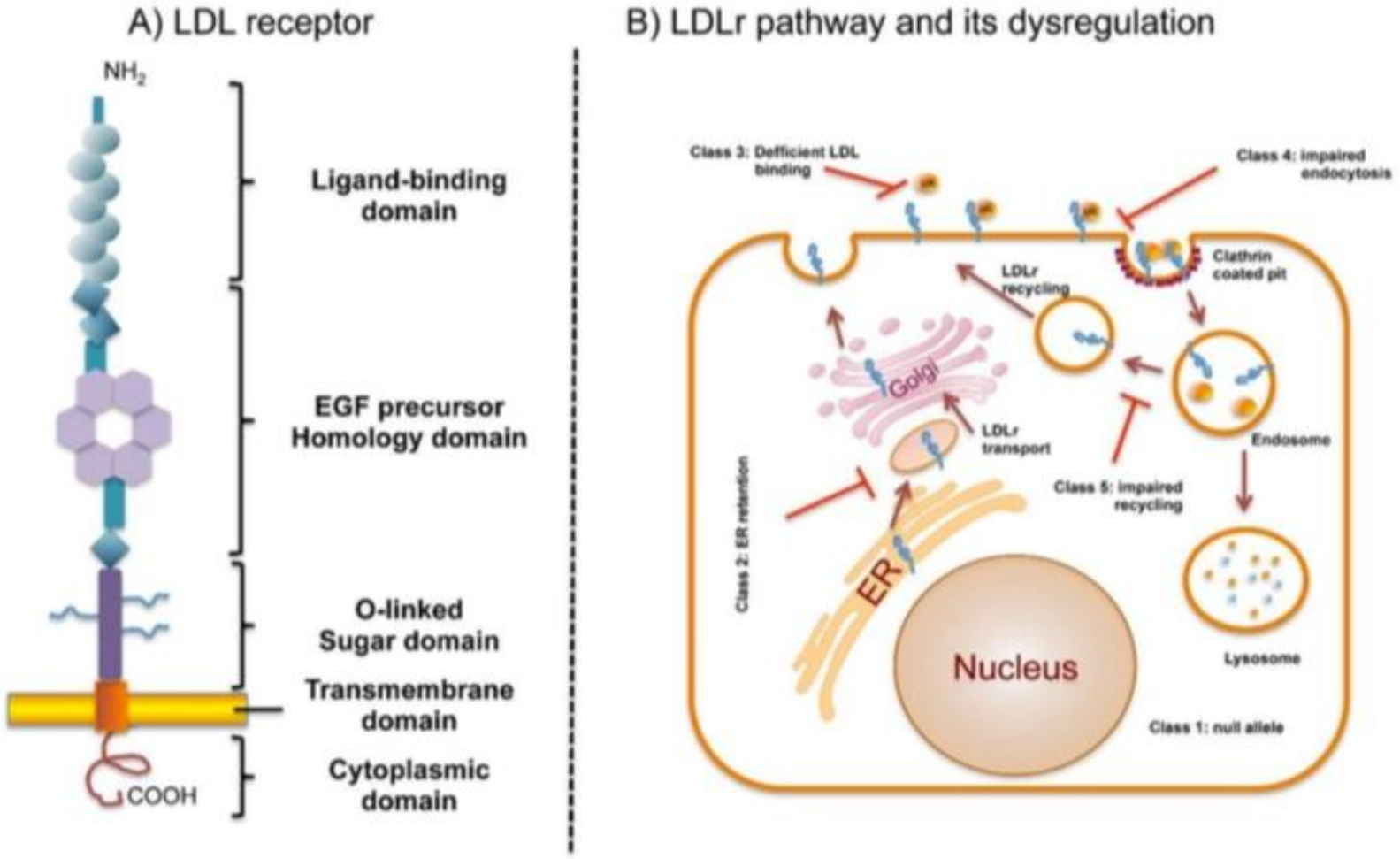
Dr Dermot Neely

Consultant Lipidologist and Specialist Adviser on Lipids to the AHSNs.

We will cover:

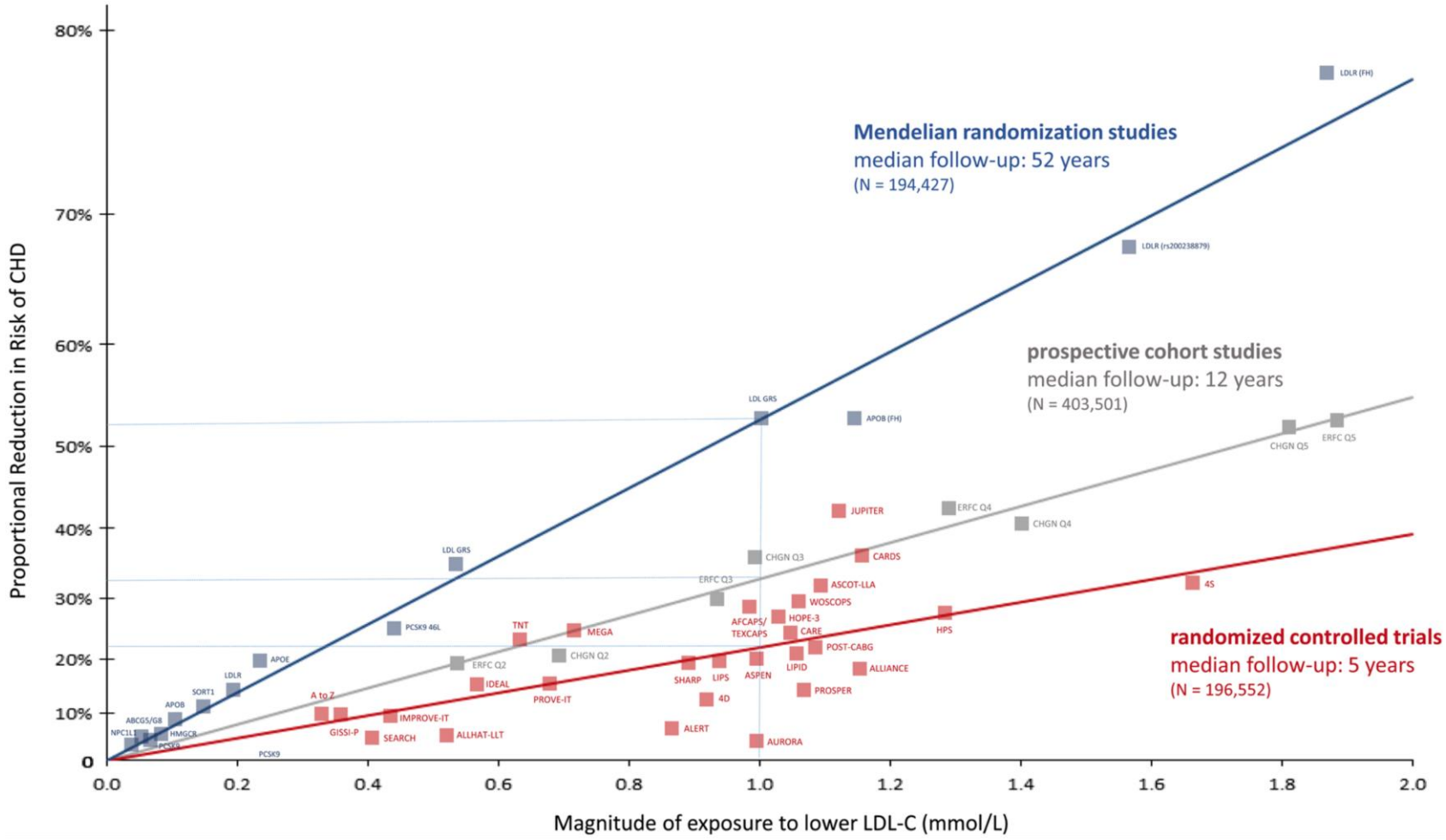
- Relationship between LDL-C and risk for CV events
- High risk conditions - ASCVD and Familial Hypercholesterolaemia
- How can we achieve lower LDL-C levels in 2021?

The LDL Receptor Pathway- - key to lipid lowering



Benito-Vicente et al. Int J Mol Sci 2018;19:1676

LDL exposure drives atherosclerotic CVD

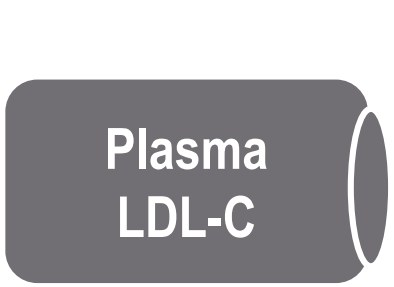


From: Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel

Eur Heart J. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

Assessing LDL-C Levels

- **Non-HDL-C levels can be used in the UK to assess and monitor CV risk; *however*:**[1]
  - Most evidence for reducing CV risk is based on LDL-C levels[2–6]
  - Access to some treatments require a measurement of LDL-C levels[7–9]



MEASURED

PREPARATIVE ULTRACENTRIFUGATION[10,11]

- **Gold standard** that provides a direct measurement of LDL-C
- **Expensive** technique that is often used in **research** settings

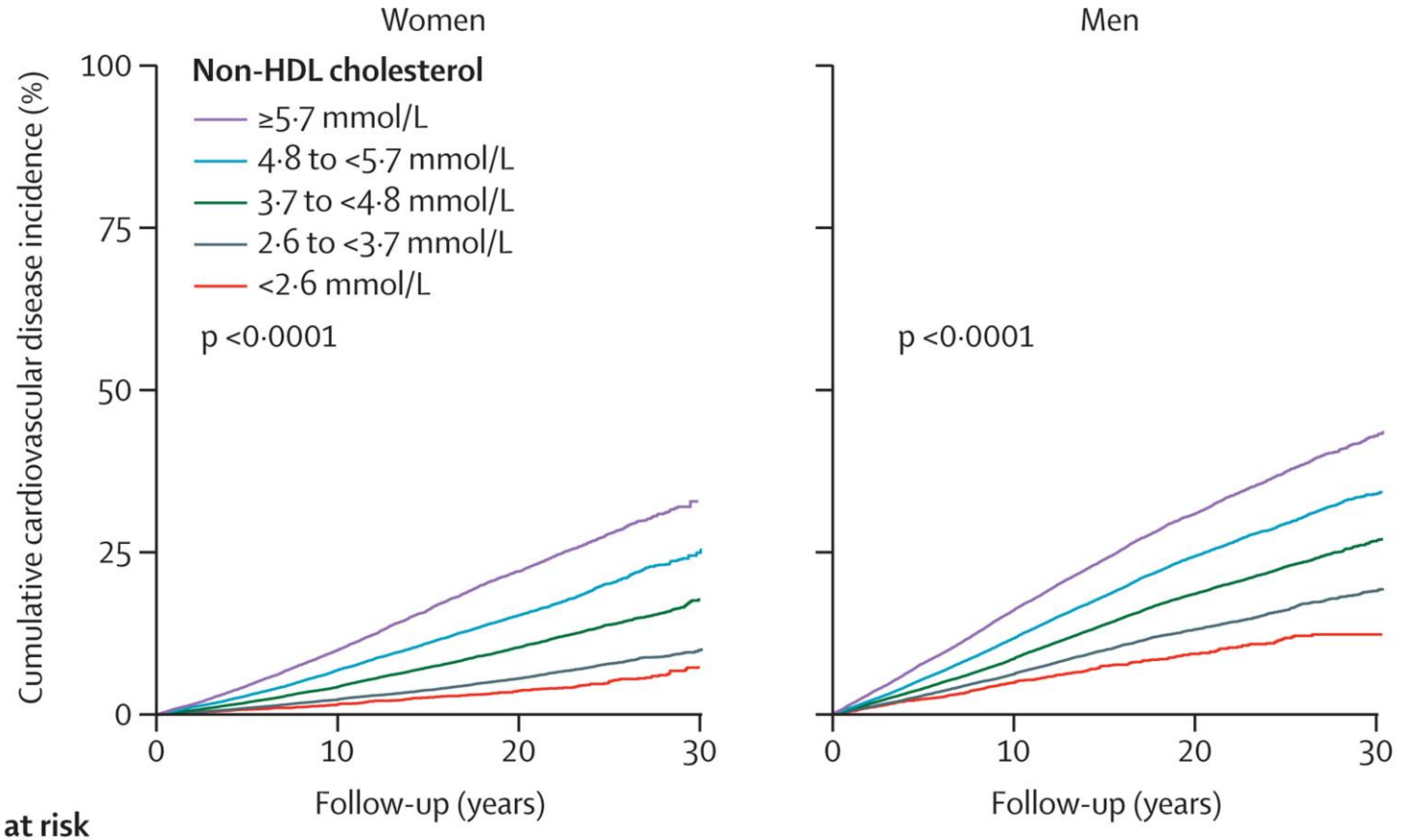
CALCULATED

FRIEDEWALD FORMULA[10–13]

- TC and HDL-C are directly measured: *LDL-C = TC – HDL-C – (TG/2.2 mmol/L)**
- **Fasting blood samples** are required for the calculation
- Can underestimate LDL-C at low levels
- Marked deviations in hypertriglyceridemia have been observed

*Only applicable if TG measure is <4.5 mmol/L, as higher values can distort LDL-C value.
CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

Cardiovascular disease and non-HDL cholesterol



Number at risk

≥5·7 mmol/L	19101	11502	3758	39	29955	17871	4036	349
4·8 to <5·7 mmol/L	26054	15534	5374	104	40190	24087	5605	358
3·7 to <4·8 mmol/L	47516	28175	10061	395	60083	34694	8810	703
2·6 to <3·7 mmol/L	46249	27712	10299	1005	37918	20743	5798	597
<2·6 mmol/L	10216	5801	2034	321	5878	2940	895	129

Brunner et al, The Lancet VOLUME 394, ISSUE 10215, P2173-2183, DECEMBER 14, 2019

Q Risk – factors amenable to an intervention

Stop Smoking

Chol/HDL Ratio

Diet

Exercise

Systolic BP

BMI

Move To A Less Deprived Postcode Area!

Scandinavian Simvastatin Survival Study Design[1]

Double-blind, randomised, placebo-controlled

- 94 centres in 5 countries
- 4444 men and women 35 to 70 years of age
- Prior myocardial infraction and/or angina pectoris
- Total cholesterol: 5.5-8.0 mmol/l
- Follow-up until approximately 440 deaths occurred
- 95% power to detect 30% reduction in total mortality

Scandinavian Simvastatin Survival Study Group, The Lancet, VOLUME 344, ISSUE 8934, P1383-1389, NOVEMBER 19, 1994

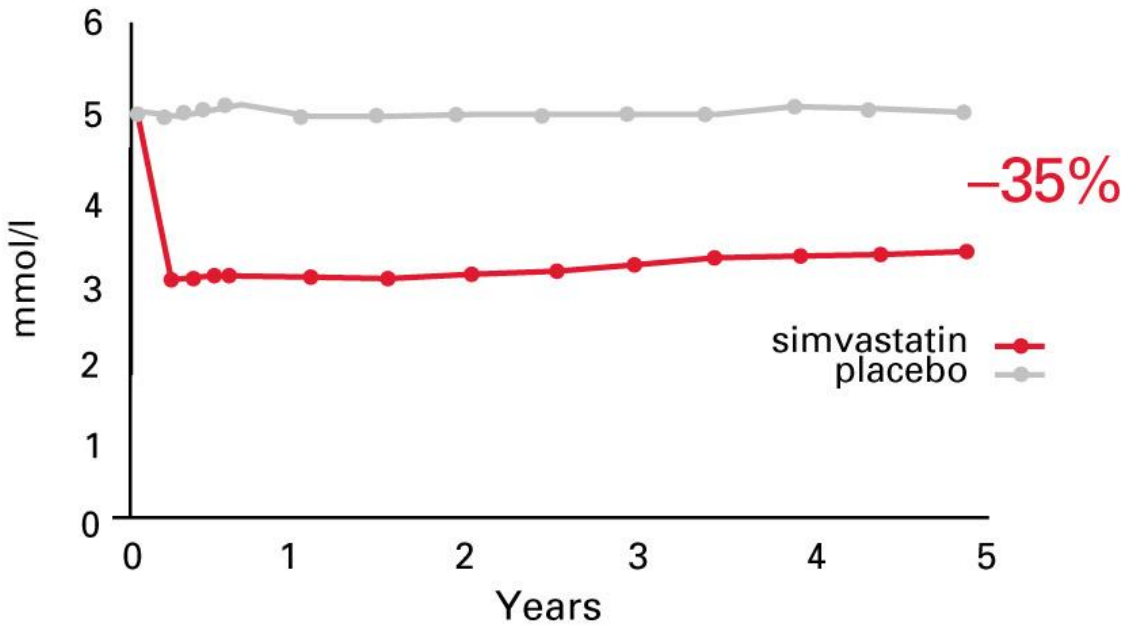
Tackling Cholesterol Together

TheAHSNNetwork ACCELERATED ACCESS COLLABORATIVE HEART UK THE CHOLESTEROL CHARITY NHS

4S Scandinavian Simvastatin Survival Study

LDL cholesterol[2]

Mean LDL cholesterol reduction



[-1.75 mmol/L]

Scandinavian Simvastatin Survival Study Group, The Lancet, VOLUME 344, ISSUE 8934, P1383-1389, NOVEMBER 19, 1994

Tackling Cholesterol Together

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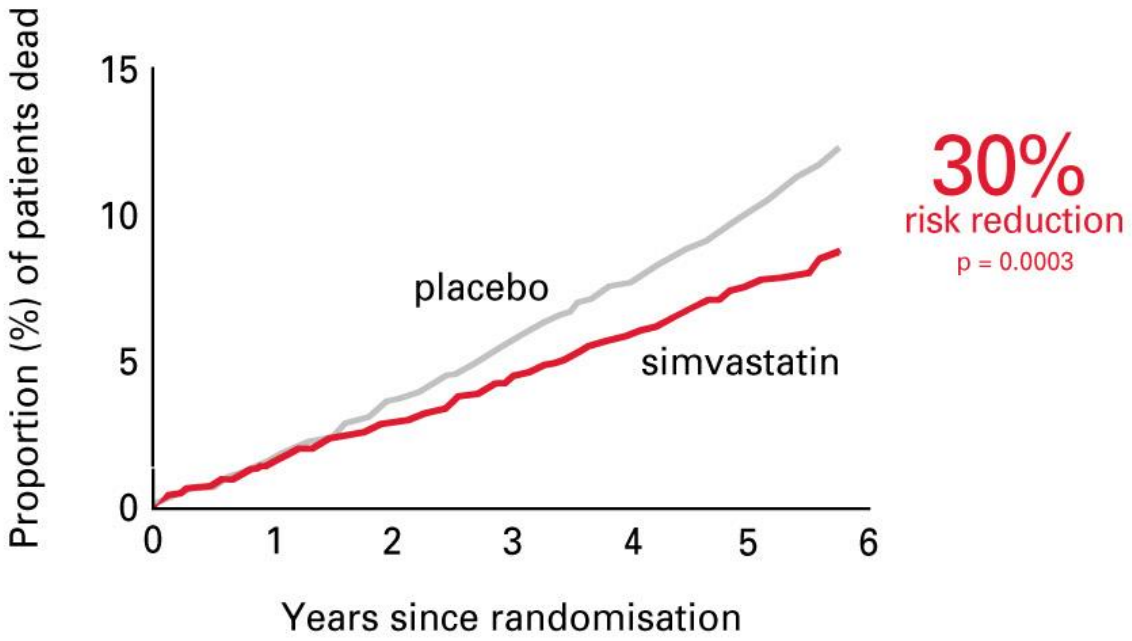
HEART UK THE CHOLESTEROL CHARITY

NHS

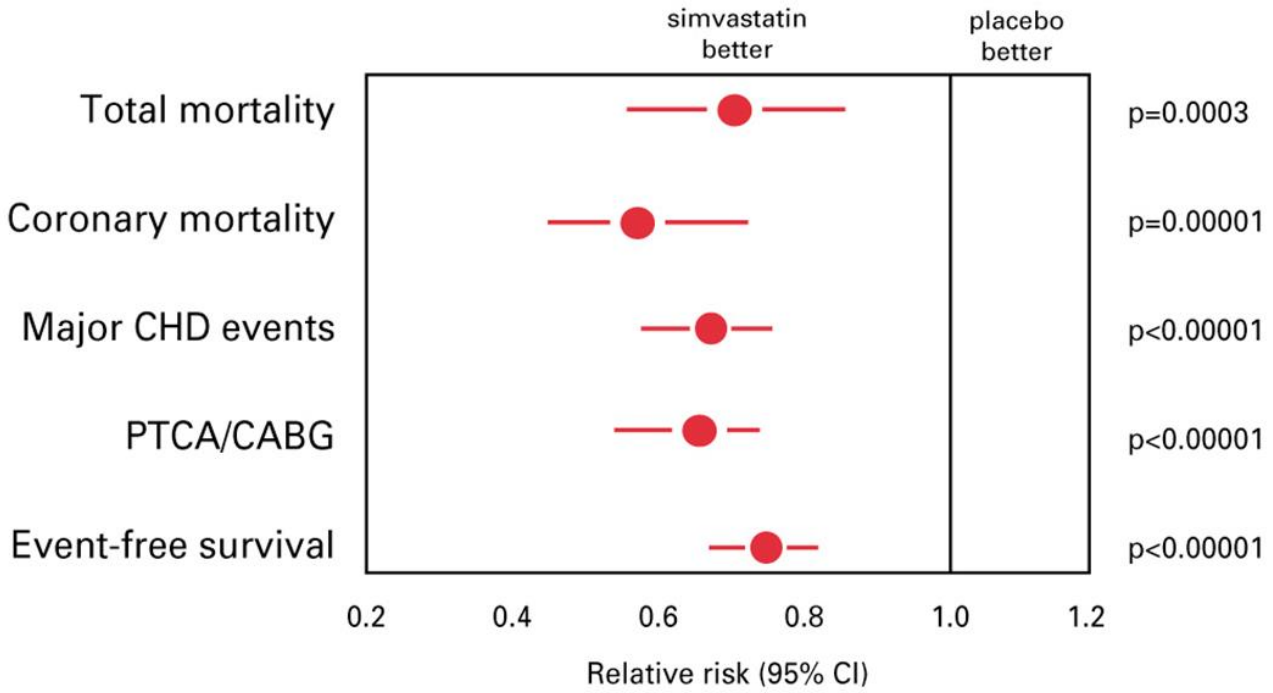
4S SCANDINAVIAN SIMVASTATIN SURVIVAL STUDY

Overall survival[1]



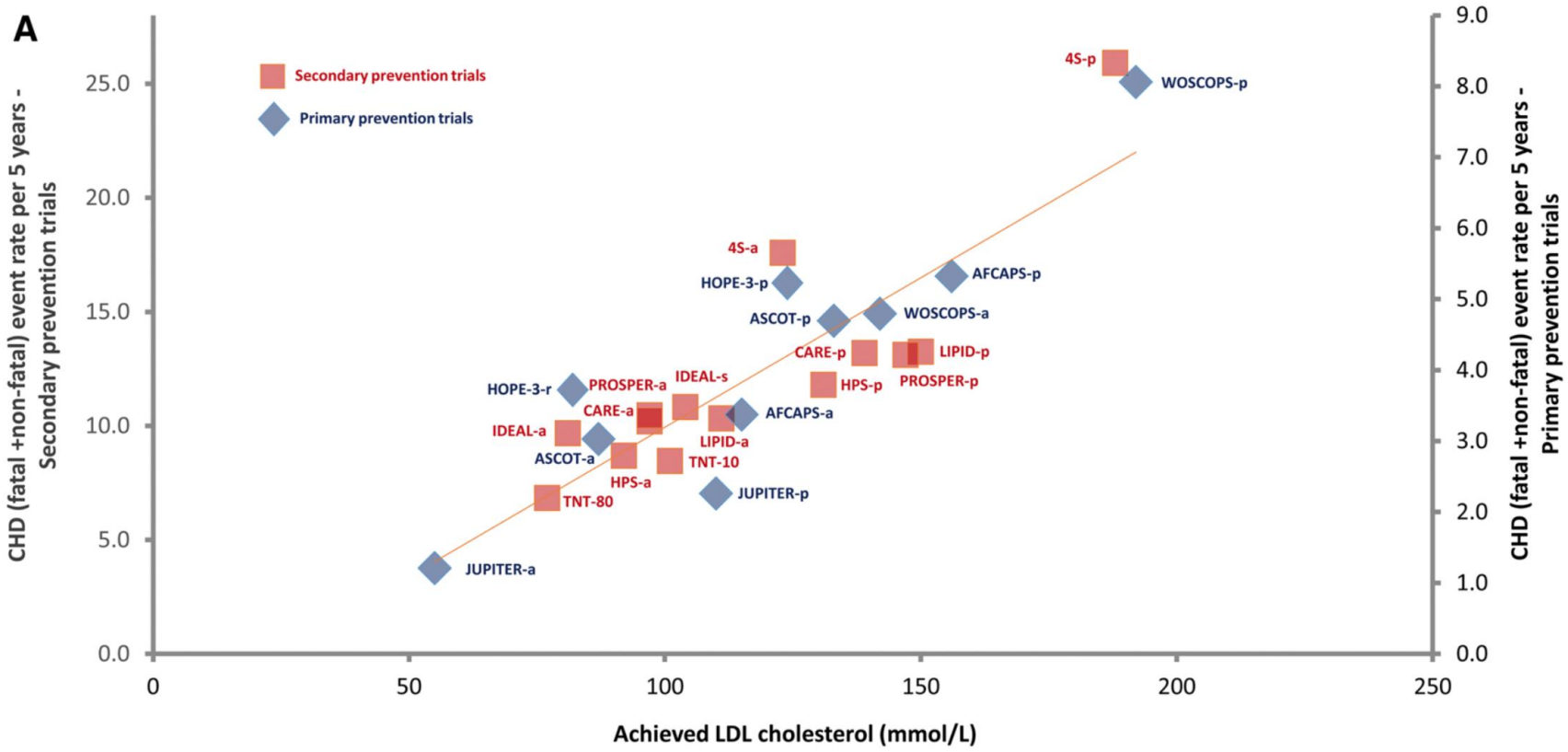
Scandinavian Simvastatin Survival Study Group, The Lancet, VOLUME 344, ISSUE 8934, P1383-1389, NOVEMBER 19, 1994

Summary of key end-point results[1,2]



Scandinavian Simvastatin Survival Study Group, The Lancet, VOLUME 344, ISSUE 8934, P1383-1389, NOVEMBER 19, 1994

Lower achieved LDL-C reduces CVD events



From: Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel
Eur Heart J. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

Familial Hypercholesterolaemia FH – a monogenic disorder of the LDL-receptor pathway

Familial hypercholesterolaemia causes lifelong elevation of LDL-C levels[1]

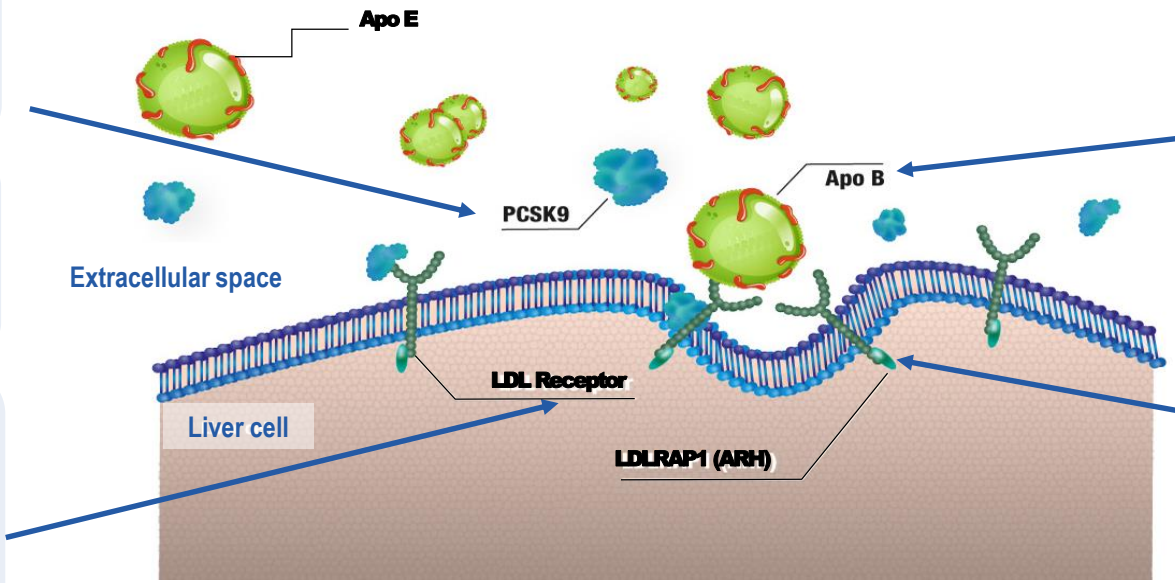
Mutations in key genes regulating LDL receptors reduces LDL uptake by hepatocytes and elevated plasma LDL-C[1,2]

Key Proteins Involved in LDL Uptake

PCSK9 binds to the LDLR, leading to LDLR degradation[2,3]

ApoE is an accessory ligand for the LDLR, assisting binding of LDL[4]

LDLR binds to ApoB on an LDL particle, inducing endocytosis of the LDL particle[2,3]



ApoB acts as a ligand for the LDLR, mediating the binding of LDL[2,3]

Internalisation of the LDLR–LDL-C complex by endocytosis is mediated by the LDLR adaptor protein, **LDLRAP1**[3]

ApoB, apolipoprotein B; ARH, autosomal recessive hypercholesterolemia; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDLRAP1, LDLR adaptor protein 1; PCSK9, proprotein convertase subtilisin/kexin type 9.

1. Nordestgaard, et al. Eur Heart J. 2013;34:3478–3490a; 2. De Castro-Orós, et al. Appl Clin Genet. 2010;3:53–64; 3. Soutar and Maoumova. Nat Clin Cardiovasc Med. 2007;4:214–225. 4. Rashidi, et al. Open Cardiovasc Med J. 2017; 11: 84–93

Characteristics of Heterozygous (HeFH) and Homozygous FH (HoFH)

	HeFH	HoFH
Genetic mutation[1]	One mutated allele	Two mutated alleles
Prevalence[2]	~1:250	1:160,000–300,000
Total cholesterol[3]	8–15 mmol/L	12–30 mmol/L
LDL-C levels[4–7]	≥5 mmol/L	>13 mmol/L
Physical presentation[4–6,8]	Xanthomas* or corneal arcus	Xanthomas* or corneal arcus in childhood
Acute MI[5,8,10]	Usually >30 years old	Early childhood/adolescence†
CHD development[3–6]	<55–60 years old	Childhood/adolescence‡

*Subcutaneous cholesterol deposits in peripheral tissues;9 †If left untreated, patients with HoFH die before the age of 20;3,6 ‡For FH homozygotes, >40% of individuals will develop CHD before the age of 20.10

CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MI, myocardial infarction.

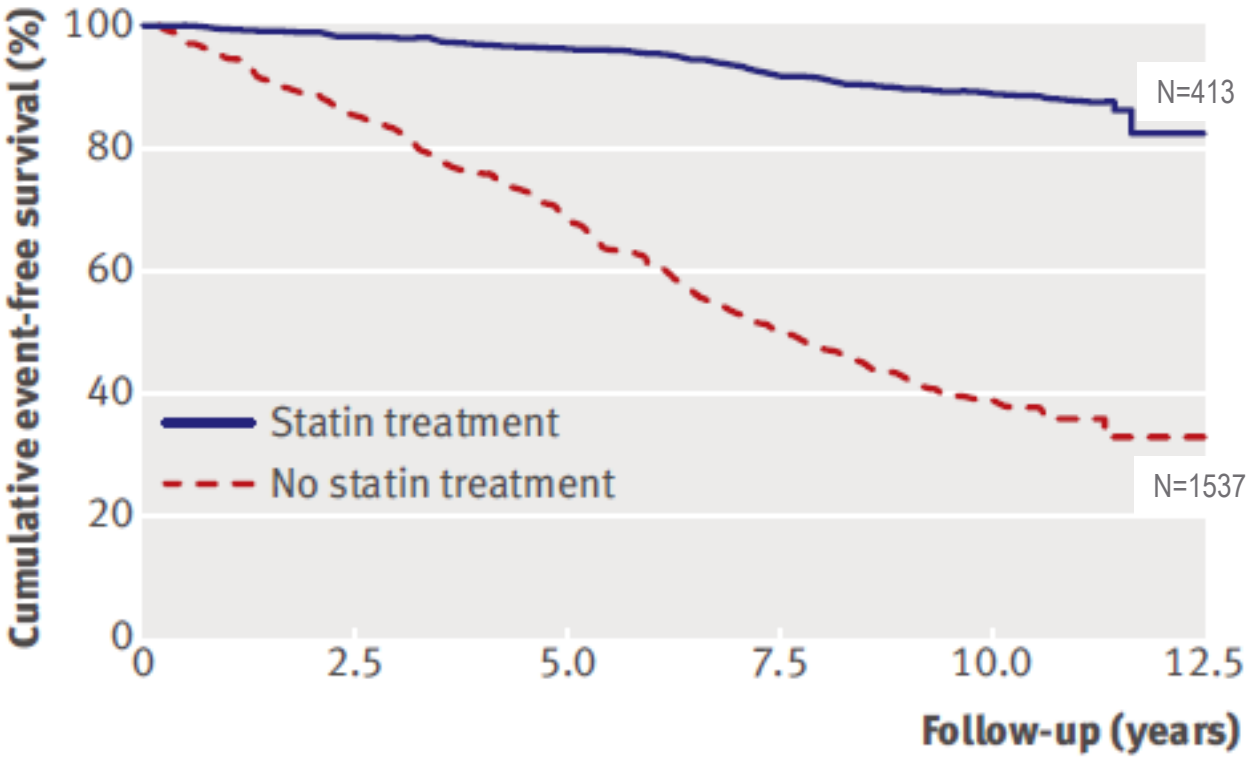
Untreated FH- risk of ischaemic heart disease

Age (years)	♂ % CHD	♀ % CHD
<30	5.4	0
30-39	23.7	2
40-49	51.4	12.2
50-59	85.4	57.5
60-69	100	74.4

Slack J. Lancet (1969) ii:1380-2

Efficacy of statins in familial hypercholesterolaemia: a long term cohort study

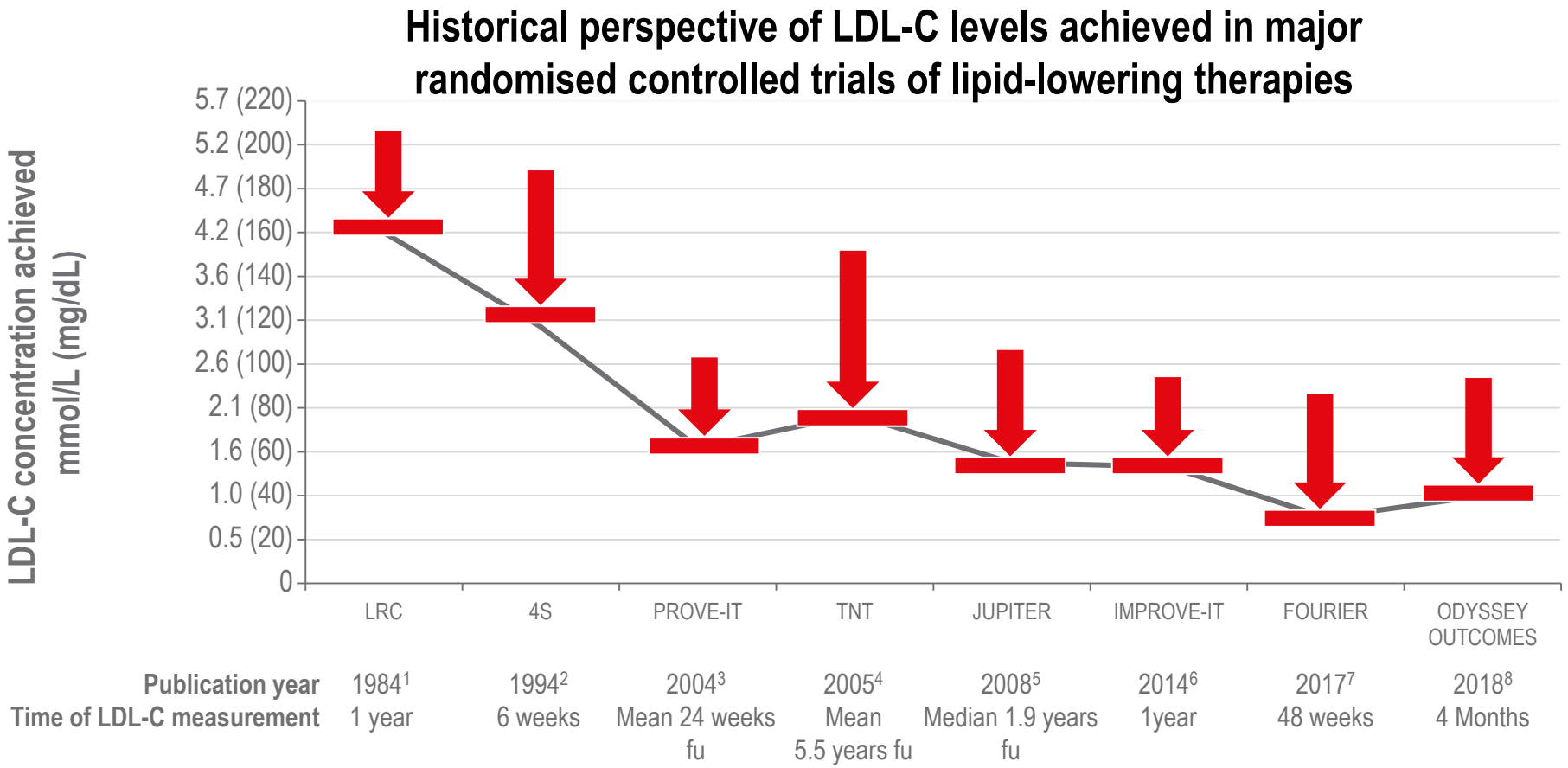
Jorie Versmissen, researcher,[1] Daniëlla M Oosterveer, researcher,[1] Mojgan Yazdanpanah, epidemiologist,[1] Joep C Defesche, senior researcher,[2] Dick C G Basart, clinician,[3] Anho H Liem, clinician,[4] Jan Heeringa, statistician,[5] Jacqueline C Witteman, professor of epidemiology,[5] Peter J Lansberg, clinician,[2] John J P Kastelein, professor of vascular medicine,[2] Eric J G Sijbrands, associate professor[1]



"We observed an overall risk reduction of 76% (hazard ratio 0.24 (95% confidence interval 0.18 to 0.30), P<0.001). In fact, the risk of myocardial infarction in these statin treated patients was not significantly greater than that in an age-matched sample from the general population (hazard ratio 1.44 (0.80 to 2.60), P=0.23)."

Versmissen J et al ; BMJ (2008) 337: 2423

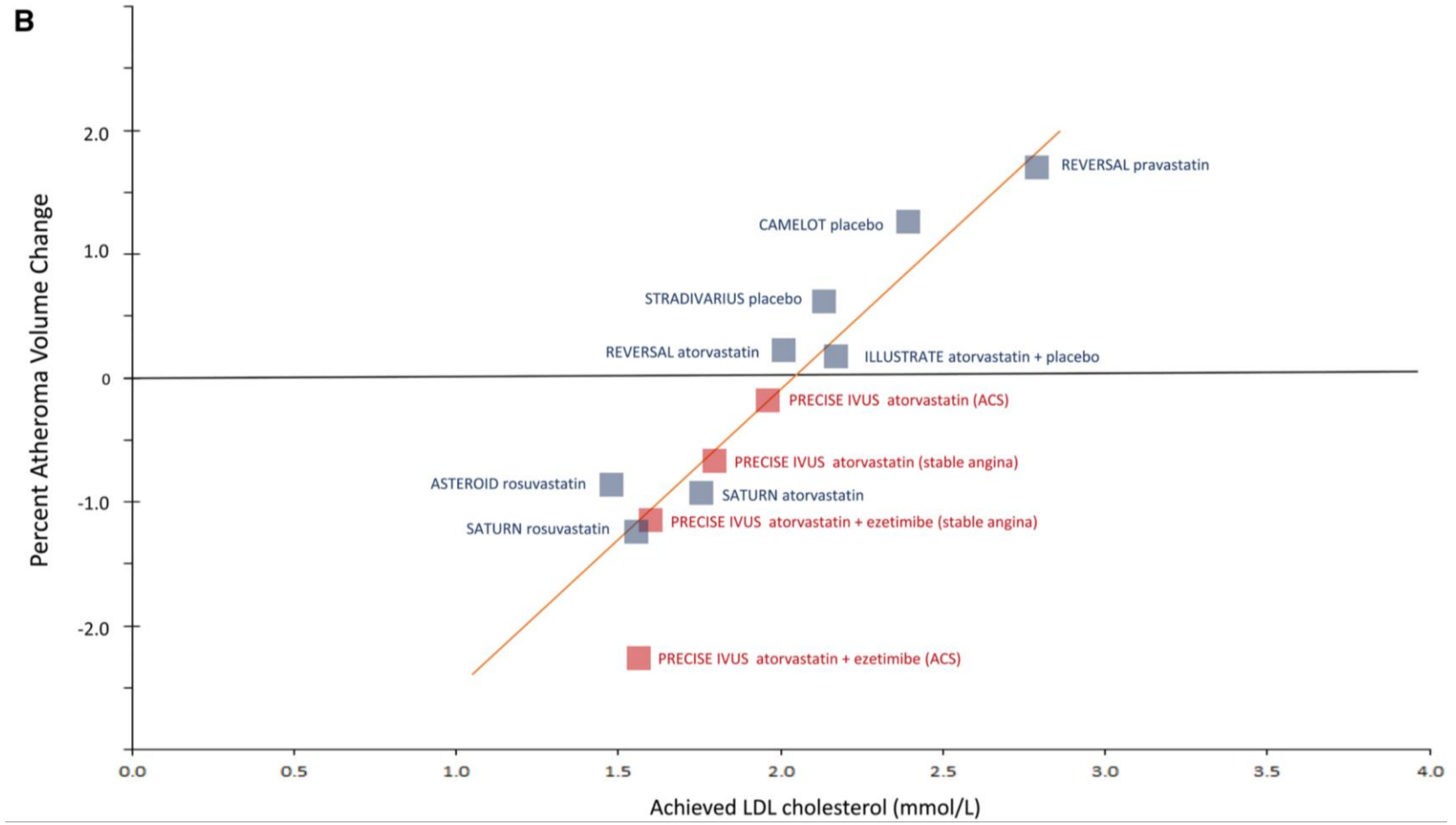
Lipid-lowering Therapies Have Evolved Over the Years to Achieve Lower LDL-C Levels

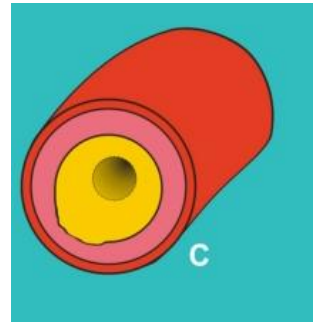


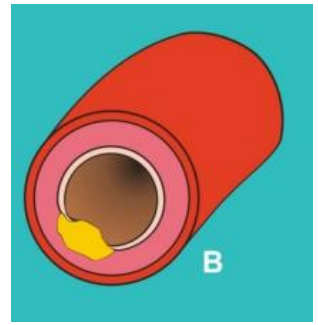
For illustrative purposes only; individual trials should not be directly compared.

Figure adapted from: Masana, et al. J Clin Lipidol. 2018;12(2):292-299.e3. Red arrows indicate the mean LDL decrease obtained in the study.
fu, follow up; LDL-C, low-density lipoprotein-cholesterol.

Lower LDL-C promotes regression







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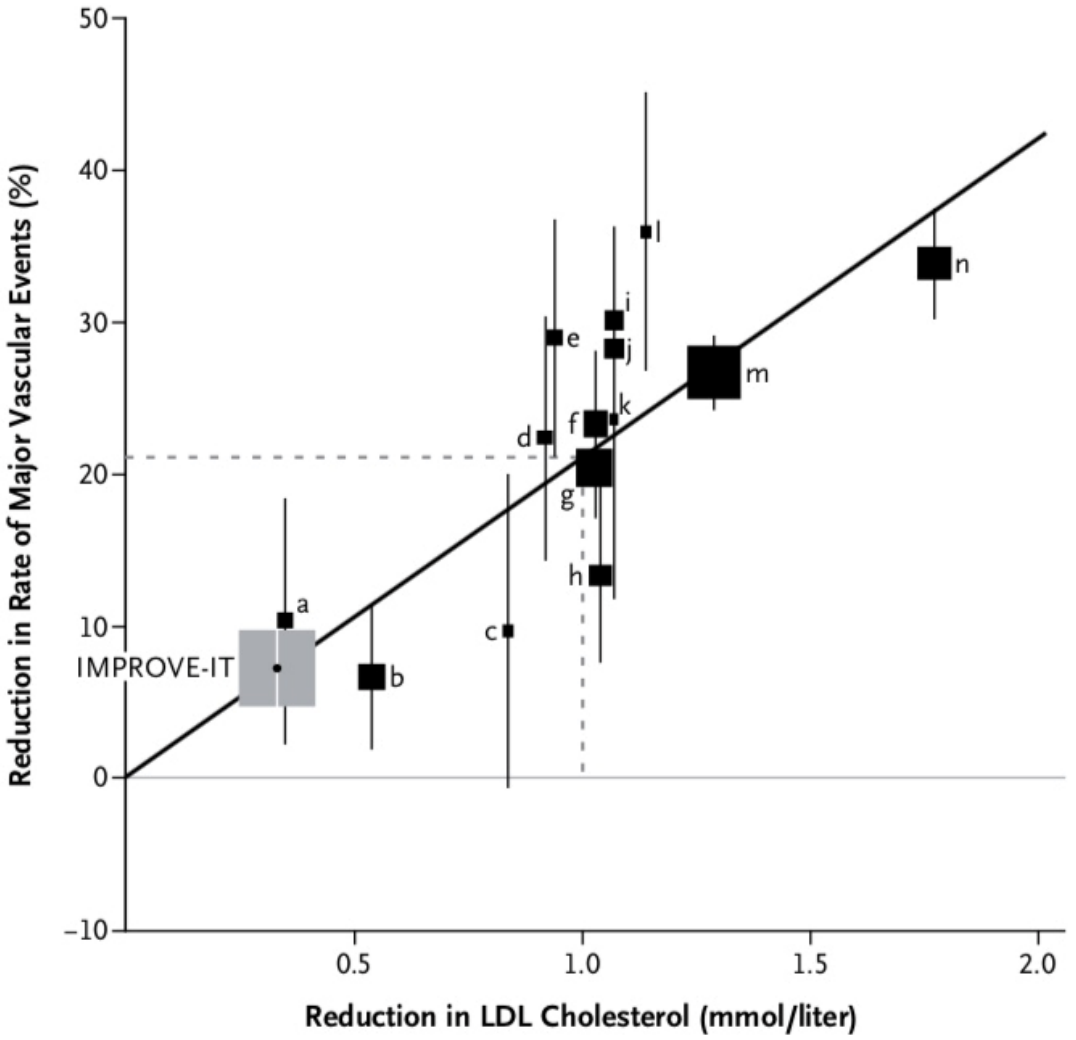
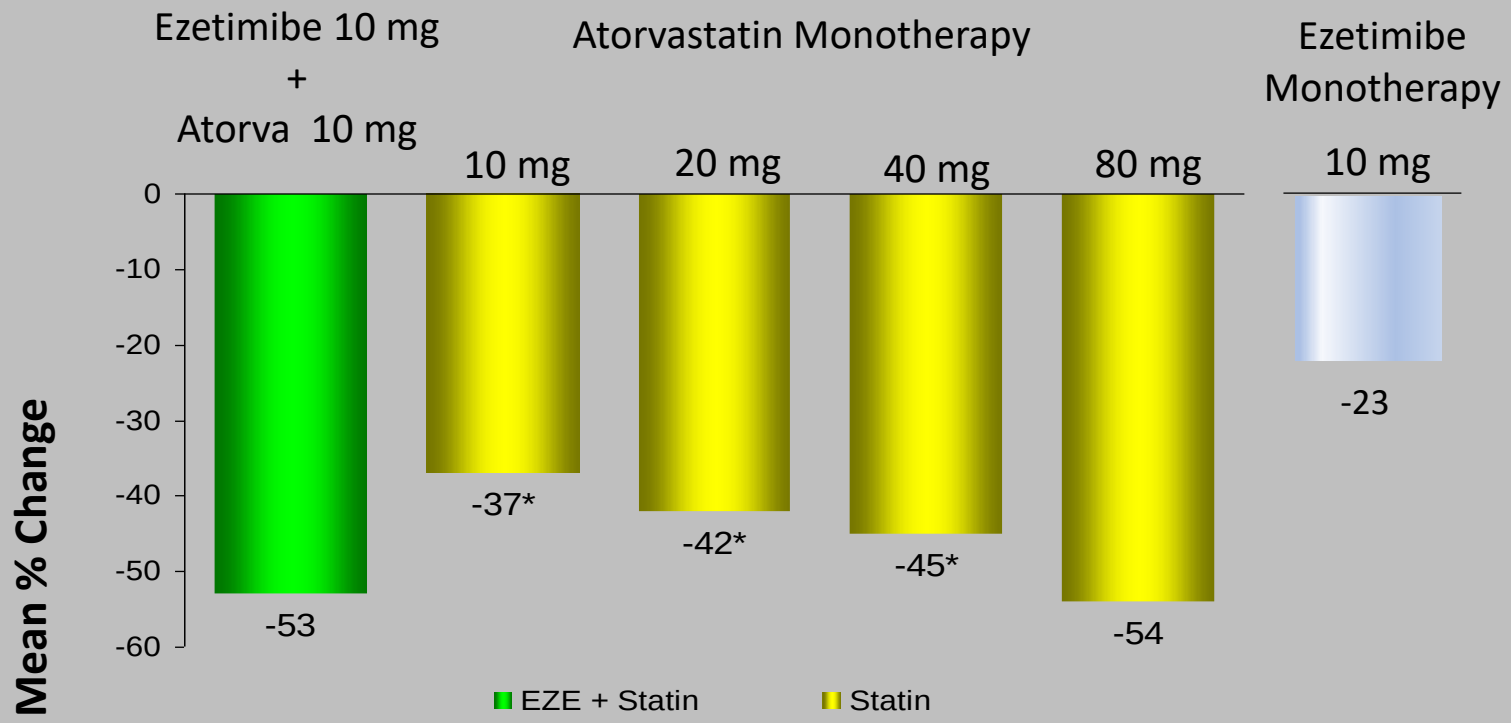
IMPROVE-IT worth adding ezetimibe to a statin?



The difference in MACE per mmol/L LDL-C is in line with statins

Cannon N Engl J Med (2015)372:2387

Ezetimibe + statin – a quick win?



* p<0.01 combination therapy versus statin alone

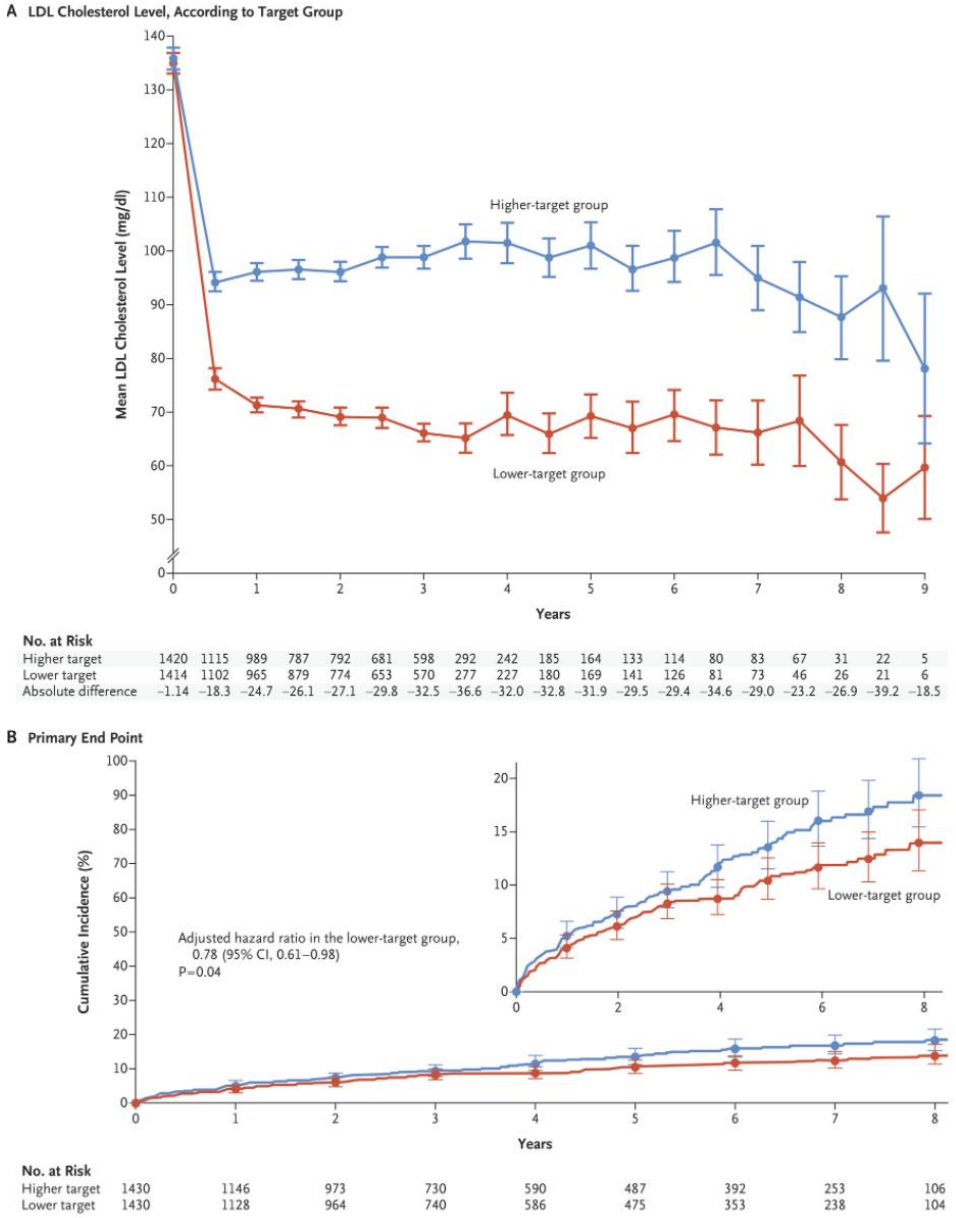
Ballantyne et al, Circulation 2003 May 20;107(19):2409-15.

A Comparison of Two LDL-C Targets after Ischemic Stroke

Titration or statin dose and/or addition of ezetimibe to achieve lower target of LDL-C

- <1.7 mmol/L vs higher target LDL-C <2.6 mmol/L reduced MACE by a further 22%

(LDL-C <1.7 mmol/L
= non-HDL-C <2.5 mmol/L)



Amarenco et al. NEJM Nov 2019

Take Home Messages

Lipid management of high risk patients in the UK remains suboptimal despite effective treatment recommended by NICE

Recommended High intensity statins (HIST) and ezetimibe are underused

Many high risk patients are on no lipid lowering therapy at all

NICE endorsed pathways summarising Lipid Management and Statin Intolerance are now available to guide lipid optimisation in practice

Non-fasting non-HDL-cholesterol replaces fasting LDL-cholesterol for monitoring and assessment of adequacy of response to therapy- with HIST we should achieve at least 40% reduction; if not consider adding ezetimibe

Where baseline lipid measurements are unavailable for setting secondary prevention targets, non-HDL-C <2.5 mmol/L can be used

Consider specialist referral for people at high risk of CVD who are statin intolerant or who remain poorly controlled despite maximum tolerated doses of statins and ezetimibe

05 Q&A

Next steps: Join us for the next webinar: NICE CG181: what's in it for me? Wednesday 18th August 1-2pm

Helen Williams
National Specialty Adviser for Cardiovascular Disease Prevention at NHS England and NHS Improvement

Dr Dermot Neely
Consultant Lipidologist and Specialist Adviser on Lipids to the AHSNs

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.

Lowering Cholesterol.

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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.

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https://www.heartuk.org.uk/tackling-cholesterol-together/home

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