





Statin Hesitancy, health investment and benefits over time

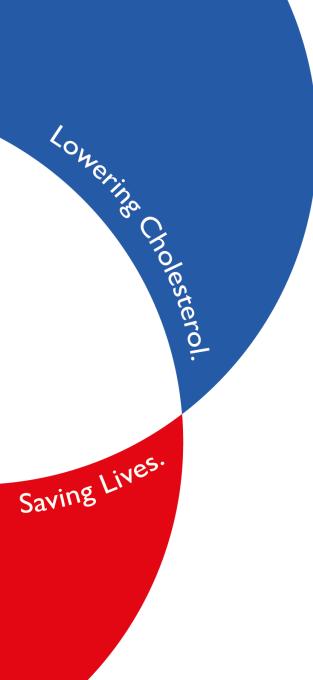
Welcome to the eighth in a series of webinars as part of the national education programme Tackling Cholesterol Together.

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

Jan 2022

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









- 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





	Topic	Presenter
01	Welcome	Sue Critchley
02	Statin hesitancy- a patient journey	Professor Terry McCormack
03	Statin Intolerance: Benefit vs Risk A balanced Evidence-Based Assessment	Professor Handrean Soran
04	Q&A. Close and next steps	Panel led by Dr Derek Connolly

Cholesterol Agenda
Together Agenda







Cholesterol

Look at hesitancy and perceived statin intolerance from the perspective of a real patient story, their experiences and beliefs

02

Objectives of today's webinar

Consider the **history** of emerging scientific evidence for LDL-C on patient outcomes

03

plan for communicating the long-term benefits of lipid lowering therapy- and combination therapy.

04

Understand what Influences LDL-C reduction, and what reduction will make a difference to outcomes.

Make sense from the literature to balance benefit/risk for patients.





CVD kills 136,000 people a year

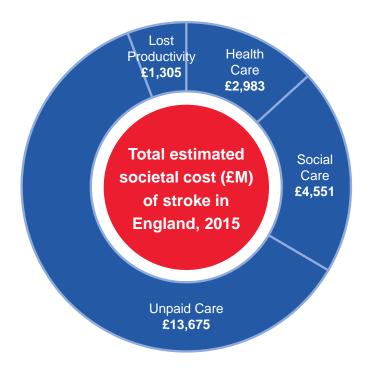
Together

CVD differentially targets
 ethnic minority communities

Why is CVD a priority?

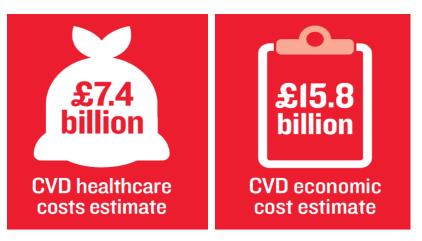
- CVD differentially targets deprived communities
- As well as death, CVD can cause significant disability
- CVD can be prevented

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





CVD Burden Remains a Significant Unmet Need across all risk factors

CVD in the UK¹

- >7 million people have CVD
- CVD has an annual total healthcare cost of £9 billion
- CVD is one of the biggest causes of death despite the availability of medical interventions and strategies

167,000 deaths/year from CVD; 44,000 are premature¹

>100,000 hospital admissions/year for an MI¹ >100,000 strokes/year¹

Up to **260,000** people in the UK have HeFH³

The NHS Long-Term Plan:²

Up to 10 year outlook for a variety of healthcare topics

- Cholesterol was highlighted for the first time in a decade
- CV risk management is a combined approach: ABC (AF, Blood pressure, Cholesterol)

Improve early detection and treatment of CVD

NHS Long-Term Plan²

Prevent 150,000 heart attacks, strokes and dementia cases

NHS Long-Term Plan²

Expand access to genetic testing for identification of FH cases to at least 25% in 5 years

NHS Long-Term Plan²

- AF, atrial fibrillation; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; MI, myocardial infarction.
- 1. BHF. UK Factsheet, August 2019. Available at: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics. Accessed November 2019;
 - 2. NHS Long-Term Plan. Available at: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf;
 - 3. NICE Clinical Guidance [CG71]. Available at: https://www.nice.org.uk/guidance/cg71/. Accessed December 2019.









Statin hesitancy- a patient journey

Professor Terry McCormack

GP & Honorary Professor, Institute of Clinical and Applied Health Research, Hull York Medical School President, British and Irish Hypertension Society





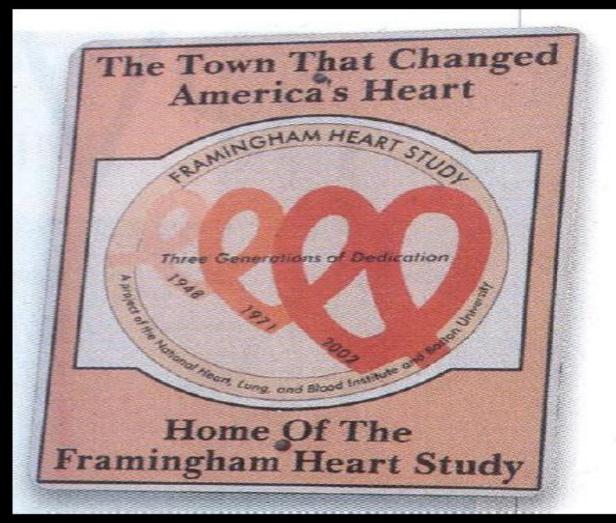
Declarations of Interest

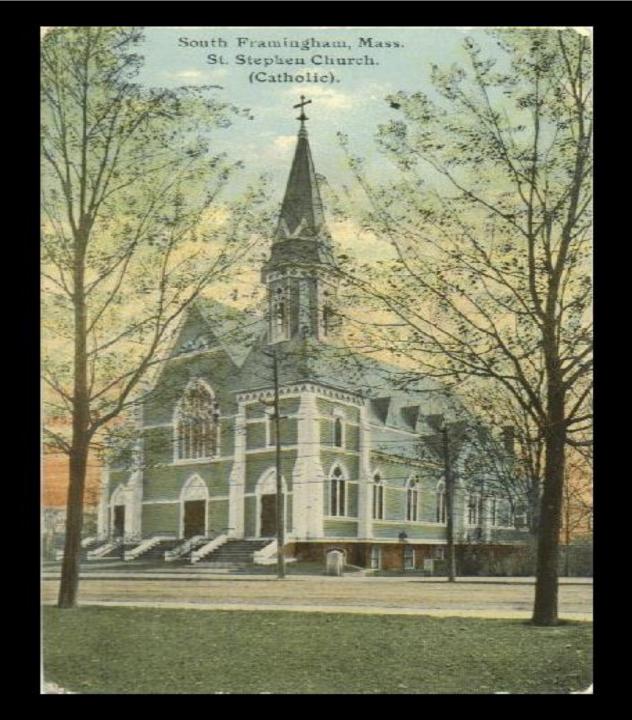
- Industry sponsorship for personal financial gain AMGEN, Bayer, Boehringer Ingelheim, Daichii-Sankyo, Novartis
- Principal Investigator Vesalius, AMGEN and CLEAROutcomes, Esperion
- SR is a real patient, who has given fully informed consent for his anonymised case history to be used



Patient SR - Male - 1987 - Age 27

- Uncle died, myocardial infarction aged 50
- Father died, myocardial infarction aged 52
- Uncle died, myocardial infarction aged 56
- All within one year of each other
- Now male cousin, died myocardial infarction aged 39
- Mixed hyperlipidaemia. Type IIb. Cholesterol raised 7.2
- Refer to dietician



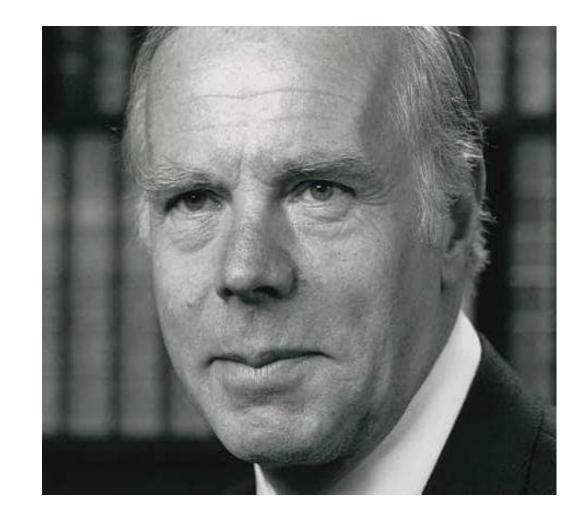




Professor Michael Oliver

(1925-2015)

- 1963 clofibrate (Atromid) fails to reduce events^{1,2}
- 1988 Reducing Cholesterol Does Not Reduce Mortality³



- 1. Oliver MF. *Lancet* 1 1,323-26 1962
- 2. Oliver MF. Symposium on Atromid. J Athererosclerosis Res 3. 351: 1963
- 3. Oliver MF. JACC Vol. 12. No 3. September 1988



Patient SR - Male - 1991 - Age 31

- Fasting total cholesterol 8.9 mmol/l
- Fasting triglyceride 1.7 mmol/l
- Frederickson type IIb
- "Refer to dietician and repeat in 3 months"
- Rx Simvastatin 10mg
- Fasting total cholesterol 6.1 mmol/l



Scandinavian Simvastatin Survival Study 19 Nov 94

- 4S
- 4444 patients
- Merck Sharpe Dohme
- Terje R Pedersen, Oslo
- Secondary prevention
- 82% male
- \$ 52% age > 60
- 622 vs. 431 CV events

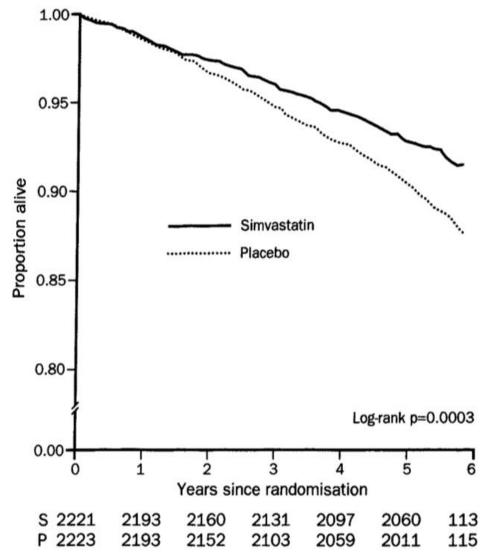


Figure 1: Kaplan-Meier curves for all-cause mortality

Number of patients at risk at the beginning of each year is shown below the horizontal axis.

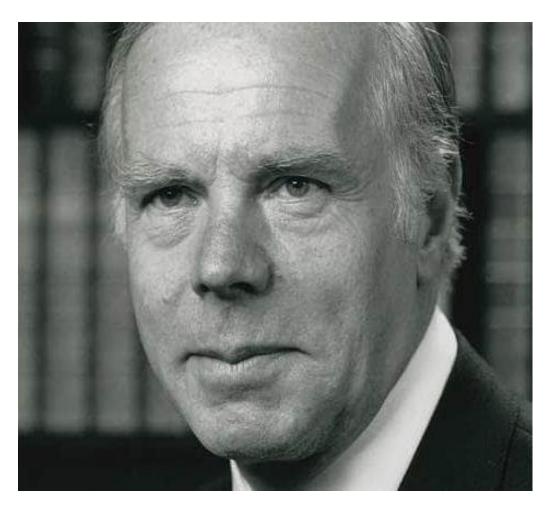
Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Scandinavian Simvastatin Survival Study Group, The Lancet, Volume 344, Issue 8934, 1383 - 1389



Professor Michael Oliver

(1925-2015)

- 1963 clofibrate (Atromid) fails to reduce events^{1,2}
- 1988 Reducing Cholesterol Does Not Reduce Mortality³
- 1996 "Lower patients' cholesterol now⁴".
- "When the facts change, I change my mind"
- 1. Oliver MF. *Lancet* 1 1,323-26 1962
- 2. Oliver MF. Symposium on Atromid. J Athererosclerosis Res 3. 351: 1963
- 3. Oliver MF. JACC Vol. 12. No 3. September 1988
- 4. Stockholm 1996





Patient SR - Male - 1994 - Age 34

- Pain in chest, arms, legs
- Creatinine kinase 114 iu/l, TC 6.4 mmol/l
- Stops simvastatin and symptoms cease
- Fasting total cholesterol 9.3 mmol/l, triglyceride 1.3 mmol/l
- HDL 1.2 mmol/l, LDL 7.5 mmol/l
- Dutch Lipid Clinical Network Score = 6 = Probable FH
- Rx bezafibrate 400mg m/r with or after evening meal
- Rx ezetimibe 10mg in 2004



Patient SR - Male - Age 61 - Taxi Driver - Problems

- Osteoarthritis acromioclavicular joint, bilateral 2020
- Non-diabetic hyperglycaemia 2018
- Non-alcoholic fatty liver 2018
- Adverse reaction to lisinopril 2010 ACE cough
- Hypertension 2010
- Nissan Fundoplication 1997
- Mixed Hyperlipidaemia 1987



Patient SR - Male - Age 61 - Taxi Driver - Medications

- Amlodipine 5mg od
- Bezafibrate 400mg m/r with or after evening meal
- Candesartan 32mg od
- Cetirizine 10mg od
- Co-codamol 30/500 two tablets qds prn
- Ezetimibe 10mg od

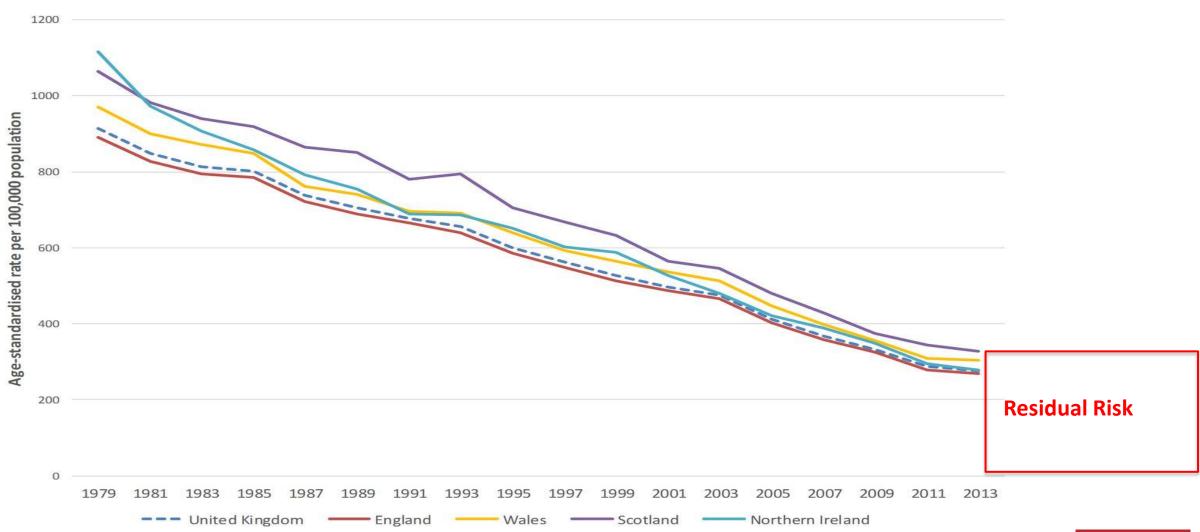


Patient SR - Male - Age 61 - Taxi Driver Most recent results

»	Date		Term	Value	Range Indicator		
shared data.)	26-Feb-2020		Serum TSH level	2.2 mU/L (0.27 - 4.20) (MF338) - Normal Advice on requesting and interpreting TFTs on Lab Med website Refer to https://tinyurl.com/BiochemInfo for further information			
	26-Feb-2020		HbA1c levl - IFCC standardised	43 mmol/mol (20 - 41) (MF338) - Abnormal - On appropriate treatment - pre-diabetes letter sent			
			Serum cholesterol	5.5 mmol/L (MF338) - Normal			
oN)			QRISK2 cardiovascular disease 10 year risk score	20.8 %			
Record	26-Feb-2020		O/E - blood pressure reading	121/79 mmHg			
Rec	26-Feb-2020		Ideal body weight	66.5 kg			
¥	26-Feb-2020		Urine protein test negative				
Ņ	26-Feb-2020		Pulse rate	82 beats/min			
	26-Feb-2020		Alcohol consumption	0 U/week			
<u>V</u> iew	26-Feb-2020		Body weight	103 kg			
	26-Feb-2020		Standing height	170 cm			
	26-Feb-2020		Bowels: normal				
	18-Sep-2019	9	Faecal calprotectin content	68 ug/g (0 - 50) (THA338) - Satisfactory			

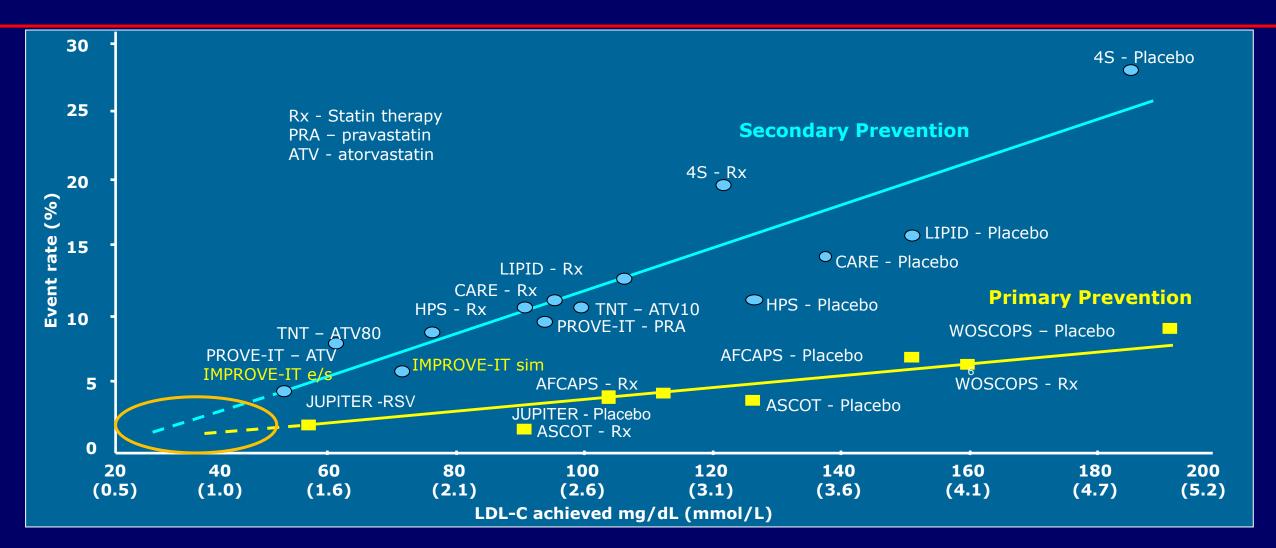


Age-standardised death rates per 100 000 from cardiovascular disease, all ages, UK and England, Wales, Scotland, Northern Ireland, 1979–2013.





Lessons from completed LDL lowering trials 'Lower is better'





CLEAROutcomes

a **CLEARProgram** study

Patient SR - Male - Age 58 - Clinical Drug Trial - 2019

Bempedoic acid 180mg/day vs placebo - Visit S2

Rash below both knees 2/7, nausea & vomit 3/7, stopped

medication 4/7

Resolved 5/7

Very surprized

Statin Intolerant Patients

4-week run-in period: treatment with Screening single-blind placebo

Visit S1 (Week-5) Visit S2 (Week-4) Visit T1 (Day 1)

25 patients, concern about lack of treatment

180 mg/day (N = 7000)

Visits at Month 1, 3 and 6; alternating phone contact and clinic visits every 3 months thereafter

> Placebo (N = 7000)

Study Completion

1620 primary 4-component MACE, at least 810 3-component MACE, and treatment for at least 2 years.













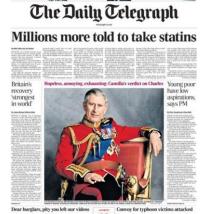


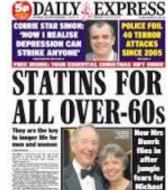
















ADDITIONAL SPECIAL



DAILY EXPRESS

ALL THE FUN, FROLICS AND

CRISIS GROWS AS

CLOSER TO WAR



The Daily Telegraph

Statins 'have no side effects'





High-dose statins 'increase Type 2 diabetes risk'





Hundreds of thousands of people on high-dose statins are increasing their chances of developing diabetes, researchers warn today.



GAUSS-3

- A trial of PCSK-9 inhibitors in statin intolerant patients
- 81% had failed to tolerate 3 different statins
- Double blind cross-over atorvastatin run in

FREE

- 26.5% could not tolerate the placebo
- 43% could not tolerate atorvastatin

Original Investigation

April 19, 2016

Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance

The GAUSS-3 Randomized Clinical Trial

Steven E. Nissen, MD1; Erik Stroes, MD, PhD2; Ricardo E. Dent-Acosta, MD3; et al

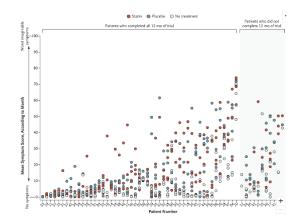
JAMA. 2016;315(15):1580-1590. doi:10.1001/jama.2016.3608





Prof Darrel Francis – SAMSON Trial - 2020

- 60 patients with statin intolerance recruited via BHF
- Randomised to 3 bottles atorvastatin 20mg placebo empty
- Symptom intensity A20 16.3% P 15.4% E 8.0%
- Nocebo effect
- 30 patients restarted statins without side effects



CORRESPONDENCE

N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects

72 Citing Articles

TO THE EDITOR:

November 26, 2020

N Engl J Med 2020; 383:2182-2184

DOI: 10.1056/NEJMc2031173

Metrics



Statin Hesitancy Game-Plan

- Shared decision making
- Mealth care provider education
- Patient education
- Pravastatin 20mg daily plus ezetimibe 10mg
- Rosuvastatin 5mg twice weekly plus ezetimibe 10mg
- Bempedoic acid 180mg plus ezetimibe 10mg (NICE TA694)
- Inclisiran in those with a history of events % LDL-C > 2.6 mmol/l (NICE TA733)



What is the ideal age to start a statin in Familial Hypercholesterolemia?

- **4?**
- **12?**
- **18?**
- **25?**
- **30?**
- **40?**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Child-Parent Familial Hypercholesterolemia Screening in Primary Care

David S. Wald, F.R.C.P., Jonathan P. Bestwick, M.Sc., Joan K. Morris, Ph.D., Ken Whyte, Lucy Jenkins, F.R.C.Path., and Nicholas J. Wald, F.R.S.

ABSTRACT

BACKGROUND

Child-parent screening for familial hypercholesterolemia has been proposed to identify persons at high risk for inherited premature cardiovascular disease. We assessed the efficacy and feasibility of such screening in primary care practice.

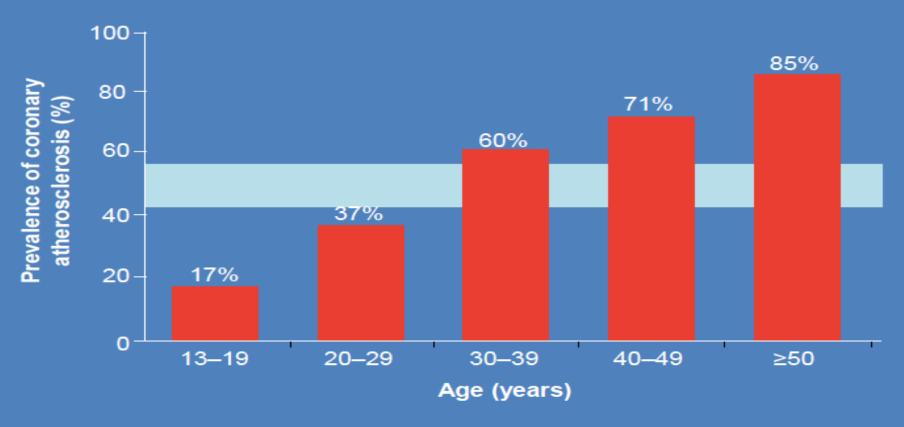
METHODS

We obtained capillary blood samples to measure cholesterol levels and to test for familial hypercholesterolemia mutations in 10,095 children 1 to 2 years of age during routine immunization visits. Children were considered to have positive screening results for familial hypercholesterolemia if their cholesterol level was

From the Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London (D.S.W., J.P.B., J.K.M., K.W., N.J.W.), and the North East Thames Molecular Genetics Laboratory, Great Ormond Street Hospital (L.J.) — all in London. Address reprint requests to Dr. Wald at the Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry,

1. Wald DS. NEJM 2016; 375:17.

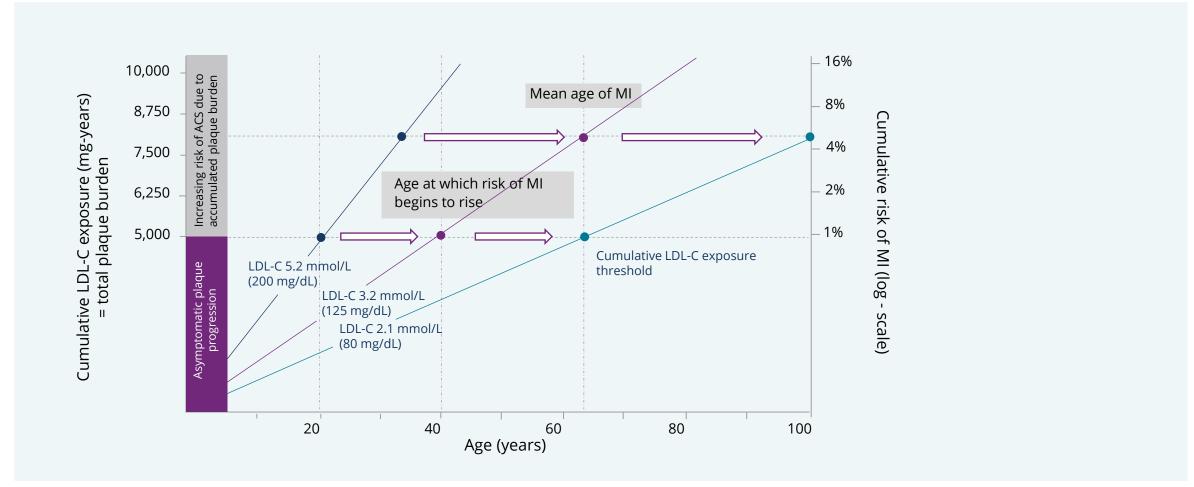
Atherosclerosis: When does it begin?¹



Data from 262 heart transplant donors.
Sites with intimal thickness ≥0.5 mm were defined as atherosclerotic.



Magnitude and Duration of LDL-C Exposure Impact ASCVD Risk¹



Adapted from Ference BA et al. J Am Coll Cardiol 2018.¹



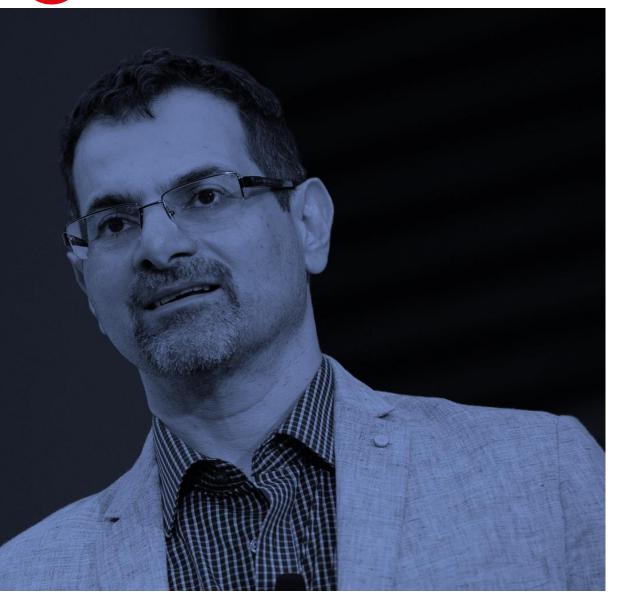




Manchester University

NHS Foundation Trust





Cholesterol

Together

03

Statin Intolerance: Benefit vs Risk A balanced Evidence-Based Assessment

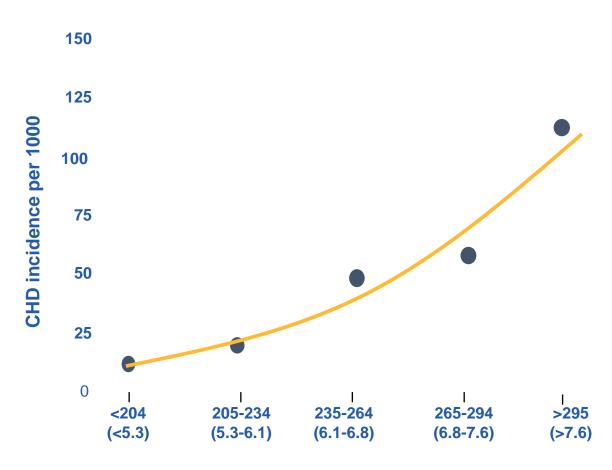
Professor Handrean Soran MSc MD FRCP

Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom



The Framingham Study: Relationship Between Cholesterol and CHD Risk

Nikolai Nikolaevich Anitschkow (1885 – 1964)



Serum total cholesterol, mg/dL (mmol/L)



Stehbens WE. Anitschkow and the cholesterol over-fed rabbit. Cardiovasc Pathol 1999;8:177-8. Finking G, Hanke H. Nikolaj Nikolajewitsch Anitschkow (1885-1964) established the cholesterol-fed rabbit as a model.

Igor E. Konstantinov, Nicolai Mejevoi, and Nikolai M. Anichkov. Nikolai N. Anichkov and His Theory of Atherosclerosis. Tex Heart Inst J. 2006; 33(4): 417–423.



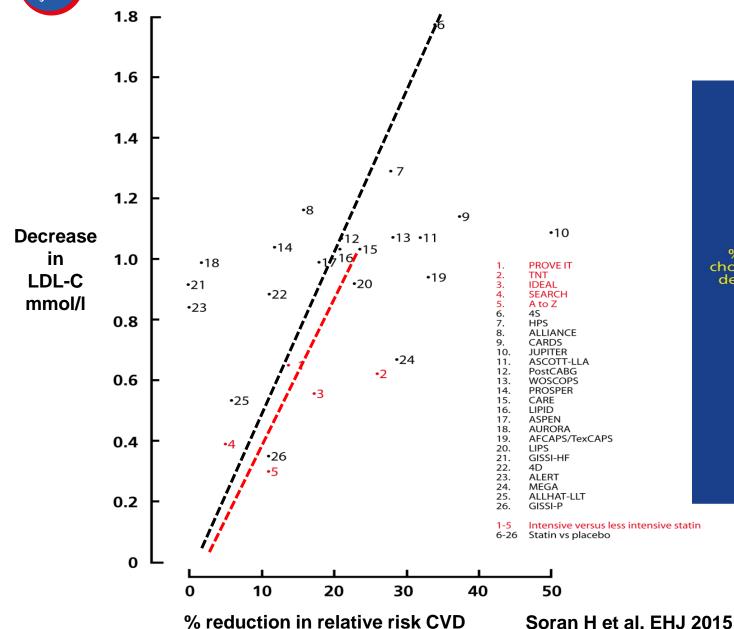
LDL-C lowering and CVD statin trials

The**AHSN**Network

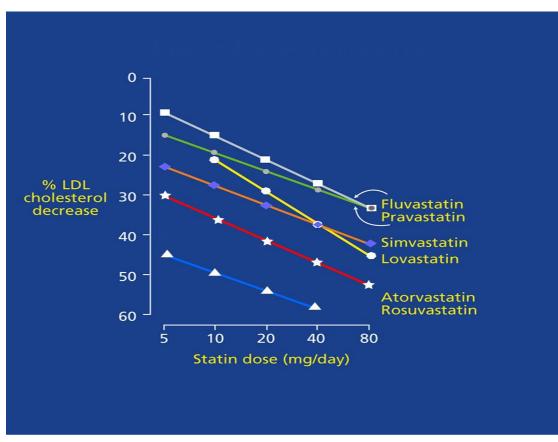
ACCELERATED
ACCESS
COLLABORATIVE







Statins potency

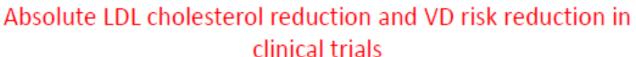


Soran H, Durrington N. Curr Opin Pharmacol 2008





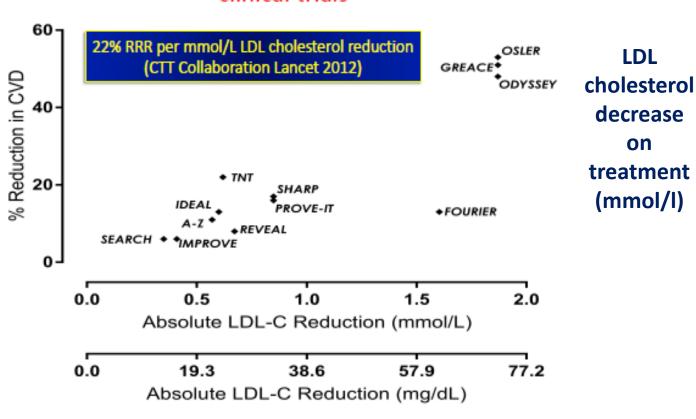
What Influences LDL-C reduction? Absolute LDL-C is what matters.

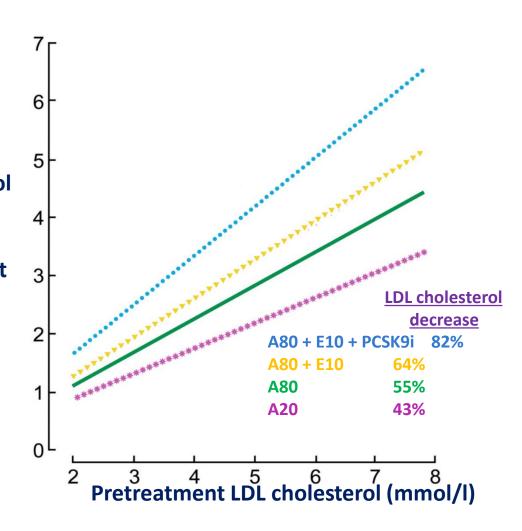


Tackling

Cholesterol

Together





Soran et al 2018

Soran H, Adam S, Durrington PN. Atherosclerosis 2018





10-year CVD **Pre-treatment LDL cholesterol**

risk	mmol/l				
	2 (-0.2,-0.86)	3_(-1.2,-1.29)	4(-2.2,-1.72) 5	(-3.2,-2.15)	5<u>(-4.2,</u>-2.58)
			<u>NNT</u>		
5%	412	78	47	36	31
7.5%	275	52	32	24	24
10%	206	39	24	18	15
20%	103	19	12	9	8
30%			6		

^{*}Number needed to treat to prevent one CVD event in 10 years calculated from NNT=100₊[(1-0.78^{LDL}) x risk] (Data derived from Soran et al EHJ 2015)

Figures in parentheses are LDL cholesterol decrease in mmol/l. Figures in red are for cholesterol-lowering treatment titrated to a target LDL cholesterol of 1.8mmol/l.

NNT* with and without LDL-C targets

The **AHSN** Network





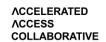


Statin Side Effects: RCTs vs Observational Studies

Cholesterol Together

- There has been considerable controversy about the true incidence of side-effects of statins and how much these impair their therapeutic effectiveness (1-14).
- On the one hand randomised controlled clinical trials report
 very low rates of even the most well authenticated side effects,
 such as myopathy (5, 6), but on the other, in uncontrolled
 observational studies, muscle symptoms are reported in as
 many as 10-20% of statin recipients (6, 9, 11, 13).

^{1.} Horton R. Offline.The Lancet. 2016. 2. Godlee F. The Lancet. 2017;389(10074):1100-1. 3. Diamond DM, et. Expert review of clinical pharmacology. 2015. 4. Hobbs FDR, et al. BMC medicine. 2016. 5. Collins R, et al. The Lancet. 2016. 6. Tobert JA, et al. Elsevier; 2016. Ganga HV, et al. American heart journal. 2014. 8. Escobar C, et al. Vascular health and risk management. 2008. 9. Stroes ES, et al. 2015. 10. Egan A, et al. NEJM 2011. 11. Mach F, et al. European heart journal. 2018. 12. Rochlani Y, et al. The American journal of cardiology. 2017. 13. Adhyaru BB, et al. 2018.







Statin Side Effects: Evidence from RCTs

Cholestero

Together

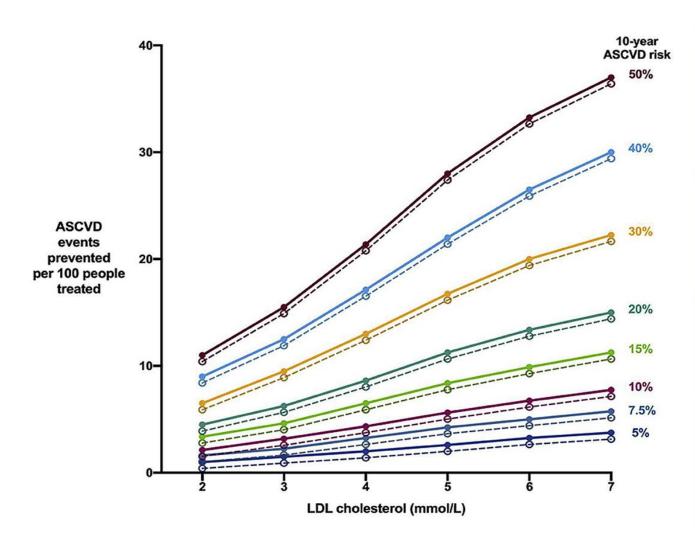
	CTT Meta- Analysis		QRISK*		SEARCH**		A-Z**	
Participants	129526		2004692		12064		4497	
Side effects 10y ⁻¹	Control s	HR	Controls	HR	Controls	HR	Controls	HR
Myopathy	0.03%	1.6	0.09%	4 †	0.03	45	0.2%	10
Liver Dysfunction	††	1	1.4%¶	1.5	0.3%¶¶	1	2%¶¶	2.3

Incidence (% over 10 years) of adverse events in controls and hazard ratio (HR) for incidence in active or more intensive statin treatment versus control. Notes: *Non-randomised observational (controls untreated with statin); ** Randomised to Simvastatin 20mg (controls) or to 80mg daily †; 2.97 in women and 6.15 in men; † †; not detected in controls or actively treated participants; ¶3xULN; ¶¶4XULN.





NNT and NNH Making sense from benefit/risk balance



The continuous lines show the number of atherosclerotic cardiovascular disease (ASCVD) events prevented per 100 people treated with statins for 10 years (N_{100}) with a therapeutic LDL cholesterol target of 50% reduction or <1.8mmol/l, whichever is lower, as a function of the pretreatment LDL cholesterol concentration at different degrees of absolute 10-year ASCVD risk.

The interrupted lines show the same but, when benefit is adjusted for harm equivalent to an ASCVD event by subtraction of 0.1333 (the number per 100 harmed (NH₁₀₀)) from the number of people avoiding an ASCVD event per 100 treated (N₁₀₀).

NNT to prevent one ASCVD is between 3 and 61 depending on ASCVD risk and pre-treatment LDL cholesterol. There is no category of patient recommended for statin treatment under current guidelines where harm outweighs benefit.

Compared with the serious consequences of not treating with statins, statin intolerance is generally mild, non-life threatening and reversible after stopping or changing the statin. Statin adverse events of potentially equivalent severity to ASCVD occur with a frequency of < 0.133% (<1 in 750) over 10 years and erode statin benefit only minimally.





Case Study

Poor statins: blamed for:

- Vitamin deficiency: Vit D, B12, IDA....
- RhA: Stiffness, attended GP, stopped statin ...,
- > Fall attended A&E, CK normal, stop statin and discharge!
- Poor mobility: Parkinson's Disease
- > OA
- Stroke/TIA
- Gout
- > MND
- And many other





Statin Side Effects: A Reasonable Approach

Statins remain the cornerstone of lipid lowering therapy and have an excellent (best) safety profile

All efforts should be made to improve compliance

Some unreasonable suggestions in the media should be resisted

which is efficacious at **low dose**, **hydrophyllic**, titrated up to a dose below which SI is not encountered.

V. If the target LDL-C has not been achieved, adjunctive ezetimibe is the next step in most patients. Consider other therapies like PCSK9 MABs, Bempedoic acid, Inclisiran....







Conclusion

- Standard accepted practice for improving control of LDL-C has evolved, but beliefs can override
- Lessons from completed LDL lowering trials provide strong evidence that 'Lower is better'. All efforts should be made to improve compliance
- Combination therapies can increase adherence and lower LDL-C closer to target
- Statins remain the cornerstone of lipid lowering therapy and have an excellent (best) safety profile









Next steps:

Join us and book for the final ninth webinar in the series:

Weds 16th Feb 2022 1-2pm

Diabetes, obesity & lipids:

Dr Derek Connolly, Professor Terry McCormack 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







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.

The **AHSN** Network

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