Lipids

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Today's Agenda

- Size of the prize and NHS Long Term Plan
- Fundamentals of cholesterol
  - Markers
  - Dyslipidaemia
- Update of NICE guidelines
  - Primary Prevention
  - Secondary Prevention
  - Familial Hypercholesterolaemia
- Treatment agents
  - Statins
  - Novel agents, including ezetimibe, bempedoic acid, inclisiran
- Treating our older patients

Size of the Prize

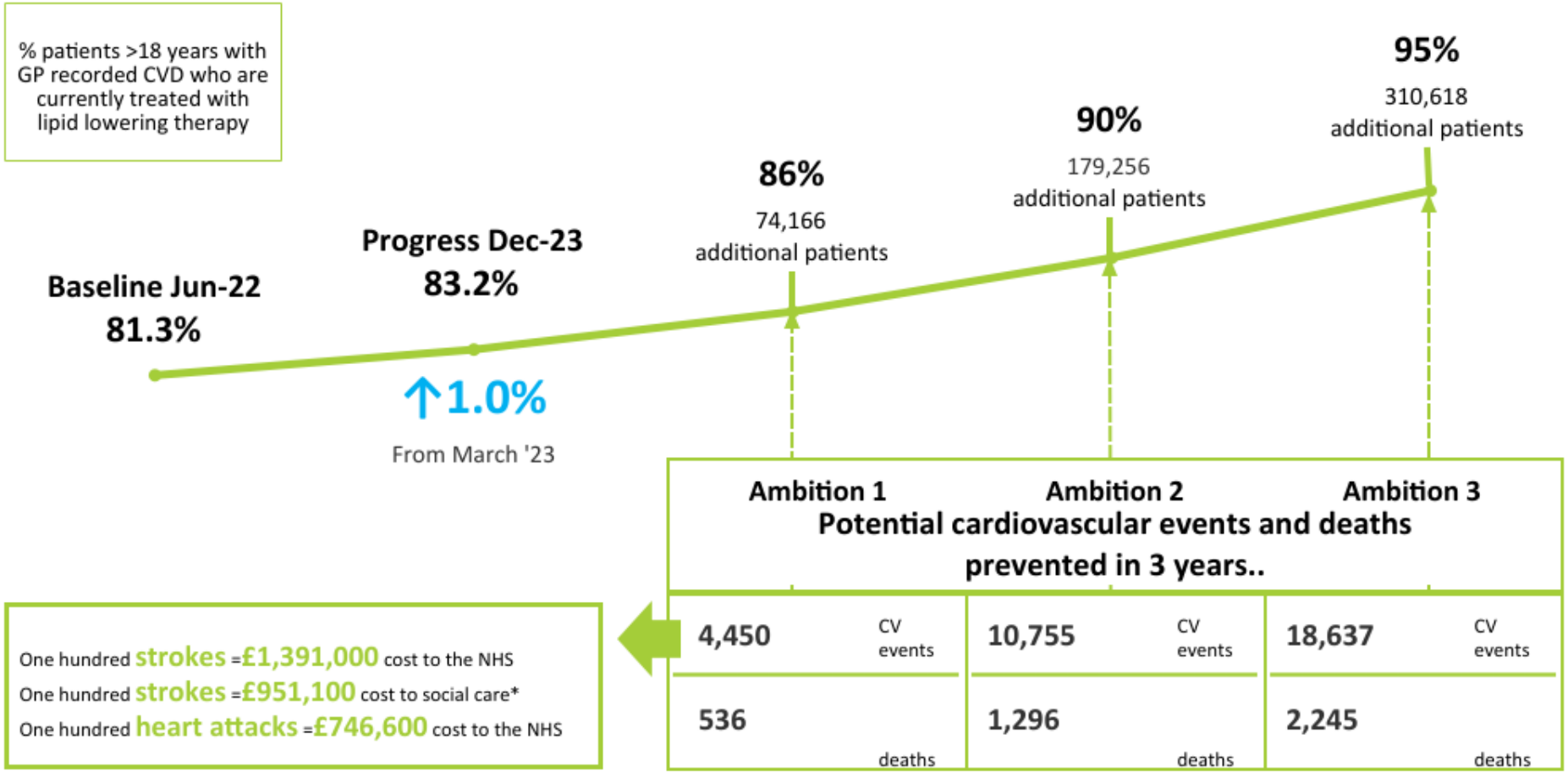
- CVD costs the NHS up to £7.4 billion per year.
- CVD is the biggest noncommunicable killer worldwide.
- One of the three ‘A-B-C’ conditions (atrial fibrillation, blood pressure and cholesterol) which are the major underlying risk factors for cardiovascular disease.
- 1mmol/L reduction in LDL-c reduces major vascular events by 22% after 1 year.

NHS Aims

- 95% of patients with established CVD should be on lipid lowering therapies
- 35% of patients with established CVD should have an LDL-c of less than 2.0mmol/L.

Size of the Prize - England
Cholesterol Optimisation to Prevent Heart Attacks and Strokes at Scale

UCLPartners Health Innovation



References

1. Collin et al. (2016), Interpretation of the evidence for the efficacy and safety of statin therapy, *The Lancet*, 388, 2532-2561. DOI: https://doi.org/10.1016/S0140-6736(16)31357-5
2. Royal College of Physicians (2016). Sentinel Stroke National Audit Programme. Cost and Cost-effectiveness analysis.
3. Kerr, M (2012). Chronic Kidney disease in England: The human and financial cost

Modelling

Data source: CVDPrevent. Briefing note: CVDPrevent online methodology annex v1 December 2022

Potential events calculated with NNT (Collins, 2016). For patients with known CVD, lipid lowering medicines for five years to prevent cardiovascular events and death: 1 in 10 for cardiovascular events, 1 in 83 for mortality.
* Stroke costs to social care are given for the 1st year following stroke only.

Cholesterol Components

Marker		"Healthy" levels
Total Cholesterol	Measured directly from blood	5mmol/L
High Density Lipoprotein (HDL-c)	Measured directly from blood	above 1.0 for a man above 1.2 for a woman
Triglycerides	Measured directly from blood	Fasting – below 1.7mmol/L Non-fasting – below 2.3mmol/L
Low Density Lipoprotein (LDL-c)	Calculated using the the Friedewald equation: LDL = TC – (HDL + TG/2.2)	Below 3 mmol/L
Non-HDL-c	Calculated from TC – HDL.	Below 4 mmol/L

LDL-c - “bad cholesterol”

Atherogenic.

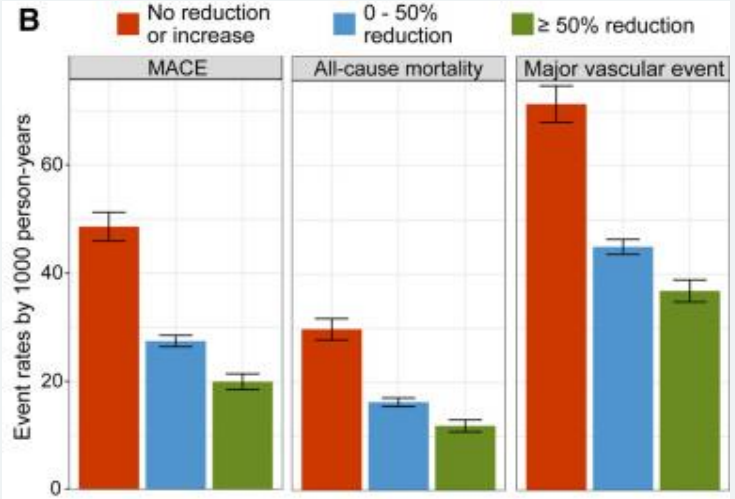
The earlier, the better.

The lower, the better.

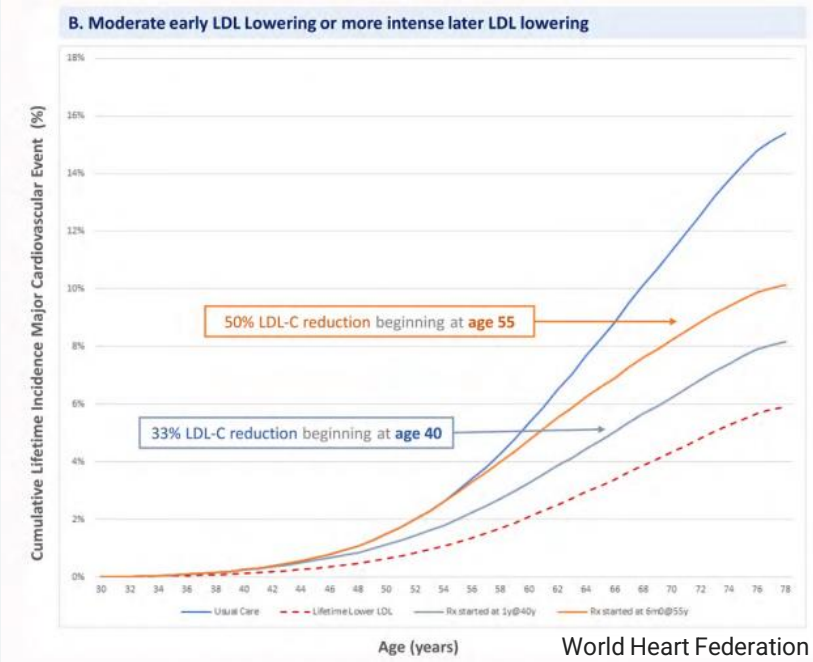
The longer the LDL-c burden, the greater the risk of plaque development.

Plaque or coronary artery calcification was present in 49.7% of people without CVD risk factors (Fernández-Friera et al, 2017).

Treatments focus on reducing this cholesterol component.



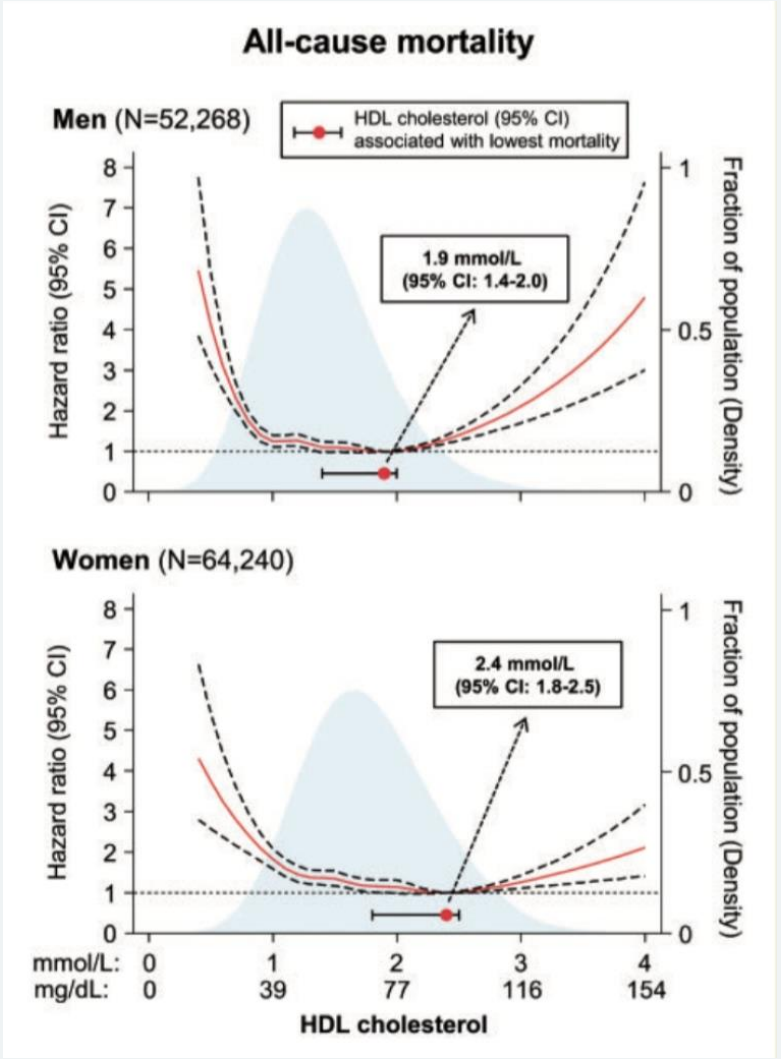
Schubert J, et al 2021.



World Heart Federation

HDL-c

- Low HDL-c levels are associated with greater cardiovascular risk.
- High HDL-c levels are associated with higher mortality.
- The current risk estimation tools may underestimate the cardiovascular risk of individuals with very high HDL-c values which may potentially lead to underuse of lipid lowering therapies (Güleç & Erol, 2020).



Madsen MC et al., 2017

Triglycerides

- Created from excess glucose which cannot be stored as glycogen.
- Typically provides energy between meals.
- Excess is carried to adipose tissue and stored.
- Metabolic changes which cause hypertriglyceridemia include a combination of triglyceride-rich lipoprotein overproduction, slower lipolysis rates and delayed clearance of particles from the circulation.
- Persistent hypertriglyceridemia is strongly associated with CVD risk in populations
- Lifestyle therapy is first line
  - QRISK>10%: Statins
  - QRISK<10% + Severe hypertriglyceridaemia: Fibrates
  - Icosapent Ethyl (Vazkepa): see BNF for more information

Category	Plasma triglyceride level (mmol/L)		Clinical correlates
Optimal	<1.2		
Borderline	1.2–1.7	VLDL overproduction	Overweight ASCVD
Moderate	1.7–5.7	VLDL overproduction plus defective clearance	Obesity Fatty liver disease Type 2 diabetes Atherosclerotic CVD
Severe	5.7–10.0	Substantially defective clearance of VLDL and chylomicrons	Obesity Fatty liver disease Type 2 diabetes Atherosclerotic CVD
Extreme	>10.0	Combined defective lipolysis of VLDL and chylomicrons	Enlarged liver and spleen Pancreatitis

Dyslipidaemia – abnormal lipids

Hyperlipidaemia – One or more raised components of cholesterol

Hypercholesterolaemia – Raised LDL-c

Hypertriglyceridemia – Raised triglyceride

Secondary Causes of Dyslipidaemia

Modifiable	Non-Modifiable
Smoking	Age
Alcohol	Gender
Sedentary lifestyle	Family History
Excessive Body weight	Ethnicity
Diet	

Secondary causes of dyslipidaemia	LDL-c	HDL-c	Trigycerides
Medication			
Excess alcohol		↑	↑
Chronic Kidney Disease			↑
Hyperthyroidism	↓	↓	↑
Hypothyroidism	↑	↑	↑
Nephrotic Syndrome (CKD with microalbuminuria)	↑		↑
Menopause	↑	↓	
Diabetes	↑	↓	↑
Obesity	↑	↓	↑

Exclude or manage secondary causes when reviewing patients presenting with dyslipidaemia

Primary Prevention Guidelines

Identify

- **QRISK > 10% OR**
- Type-1 Diabetes with one or more: age>40, >10 year duration, nephropathy, other cardiovascular risk factors,
- Chronic Kidney Disease
- HIV over the age of 40
- Age 85 or over – consider life expectancy, co-morbidities and frailty
- Familial Hypercholesterolaemia

Treat

- High Intensity Statin: Atorvastatin 20mg or Rosuvastatin 10mg
- Where lifestyle changes ineffective or not suitable

Aim

- Reduction of LDL-c by 40%
- No baseline: consider aiming for same target as secondary prevention

Optimise

- Increase Statin to Maximum tolerated
- Ezetimibe 10mg as additional (or alternative therapy for statin intolerance or contraindication)
  - Ezetimibe + Bempedoic Acid for Statin Intolerance/contraindication

NICE Secondary Prevention Guidelines

Identify

Patients with established Atherosclerotic Cardiovascular Disease:

- Coronary Heart Disease
- Peripheral Arterial Disease
- Stroke/TIA

Treat

High dose, high intensity statin: Atorvastatin 80mg or Rosuvastatin 20mg

Aim

LDL-c ≤ 2.0mmol/L or lower (non-HDL-c ≤ 2.6mmol/L where LDL-c unavailable)

Optimise

Shared decision

LDL-c under 2.5mmol/L

- Ezetimibe 10mg

LDL-c ≥ 2.6mmol/L

- Inclisiran
- Ezetimibe 10mg

Intolerance or Reluctance

- Follow national statin intolerance pathway

Familial Hypercholesterolaemia

- Autosomally dominant inherited lipid disorder
- Elevated LDL cholesterol levels from birth
- Children with FH show an increased thickness of their arteries compared to their non-FH siblings by the age of 11
- Men have a 50% chance of coronary heart disease before 50 years
- Untreated women have a 30% risk before 60 years.

- Under-diagnosed in the UK population.
  - About 220,000 people in the UK have FH, of whom **less than 8%** are currently identified.
  - A practice with a list-size of 10,000 may have 40 patients with FH.

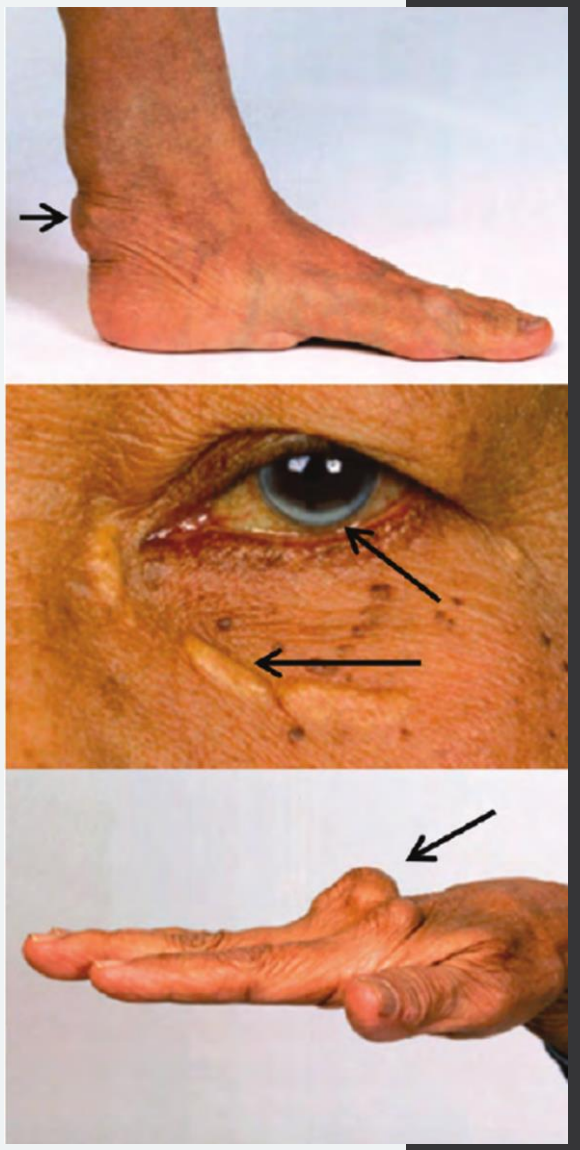
- **Target: 50% LDL-c reduction from baseline**

Suspecting Familial Hypercholesterolaemia

- A face-to-face assessment is recommended when suspecting FH.
- Ask patient to investigate their family history, including risk factors.
- Exclude or manage causes of dyslipidemia.
- Review patient's historical lipid results. Has it always been high?
- Simon-Broome Criteria
  - Fasting Cholesterol >7.5 mmol/L or LDL-cholesterol >4.9 mmol/L in adult
  - Fasting Cholesterol >6.7 mmol/L or LDL-cholesterol >4.0 mmol/L in a child under 16

  PLUS
  - Family History
    - MI before 50 years of age in a 2nd degree relative or below age 60 in a 1st degree relative
    - Raised cholesterol: >7.5 mmol/L in adult 1st or 2nd degree relative or >6.7 mmol/L in a child or sibling aged <16 years

  OR
  - Xanthomas in patient OR 1st/2nd degree relative.
- Refer once secondary causes excluded/managed and patient meets above criteria.



Statins

- HMG-CoA Reductase Inhibitor: reduces cholesterol synthesis and increases LDL receptor activity
- Has additional effects – may stabilise plaques and promote anti-inflammatory mechanisms
- High Intensity (40%+); Medium Intensity (30-40%); Low Intensity (20-29%)

Reduction in low density lipoprotein cholesterol					
Dose (mg/day)	5	10	20	40	80
Fluvastatin	–	–	21%	27%	33%
Pravastatin	–	20%	24%	29%	–
Simvastatin	–	27%	32%	37%	42%
Atorvastatin	–	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	–

Intolerance, Nocebo or Reluctance?

The presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

Statin discontinuation or intolerance is significantly associated with negative media coverage.

Large statin meta-analysis showed between 6-9% true intolerance, which is lower than some anticoagulants and antihypertensives (Bytyçi, 2022).

Statin Intolerance is over diagnosed by clinicians.

Patients require a thorough assessment when presenting with intolerance.

Source: x.com

“Muscle aches and pains”

Statin related Muscle Toxicity (SRM):
Symmetrical pain and/or weakness in large proximal muscle groups, worsened by exercise.

Risk factors for intolerance:

- Female gender
- Advanced age (> 75 yrs)
- Frailty (reduced lean body mass)
- History of muscle disorder or high CK
- Impaired renal or hepatic function
- Personal or family history of intolerance to lipid-lowering therapies
- Hypothyroidism
- Excessive alcohol intake
- High intensity exercise
- Dehydration
- Drug interactions with statins (including herbal medicines)
- Vitamin D deficiency

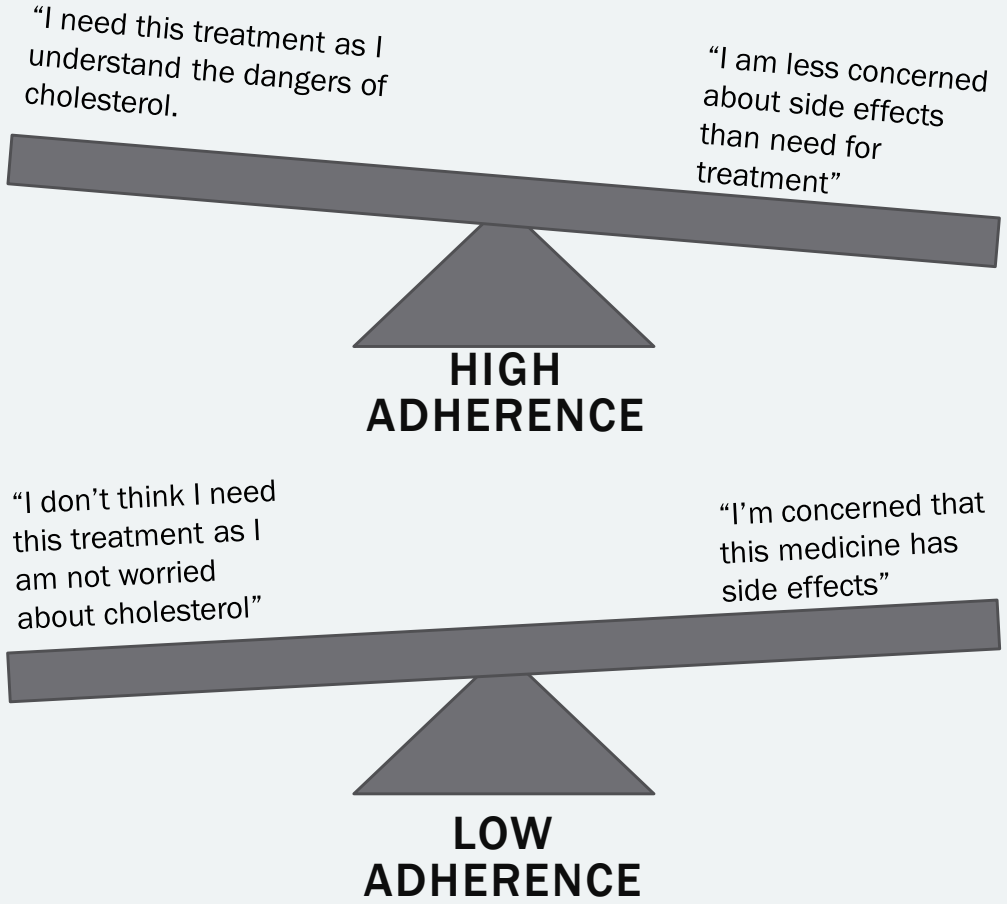
Tackling Reluctance, Intolerance or Nocebo

1. Identify if this is true intolerance or nocebo by following the NHS Statin intolerance pathway.

2. Aim to tilt their scales to high adherence. Decision Aids are effective in improving adherence (Cochrane 2024).

3. Consider starting at low doses or alternative therapies, such as ezetimibe.

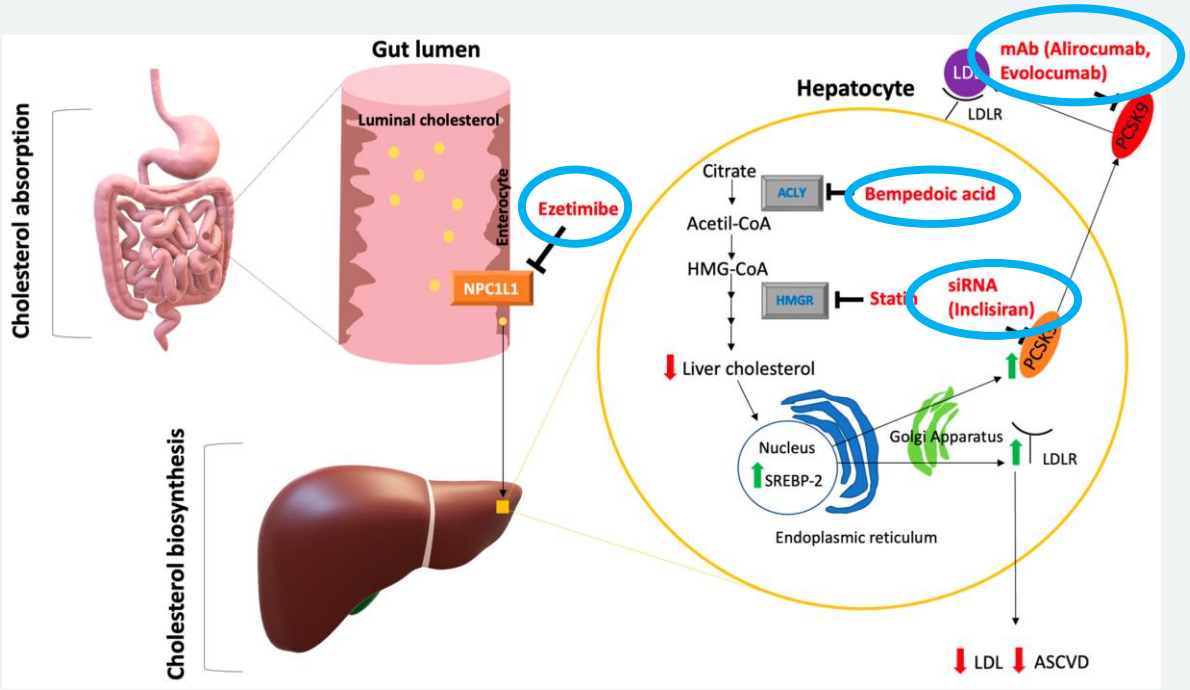
Statin	Type	
Atorvastatin	Lipophilic	• **Long half life** – Try once a week and increase every 2-4 weeks.
Rosuvastatin	Hydrophilic	• **Long half life** – try once a week and increase every 2-4 weeks.
Pravastatin	Hydrophilic	• Low intensity Statin
Simvastatin	Lipophilic	• 80mg not recommended due to myopathy risk.



Novel therapies

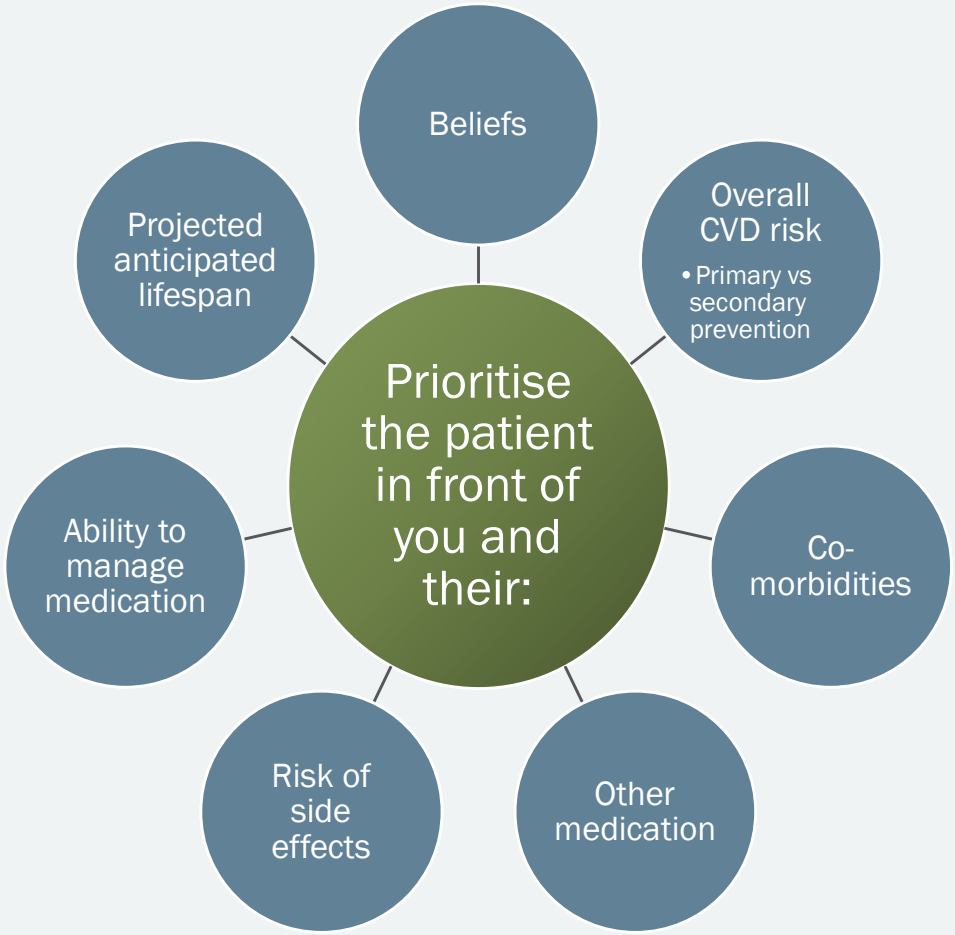
- Used when LDL-c goal not met or confirmed intolerance/contraindications to first line therapies.

- **Bempedoic Acid** inhibits adenosine triphosphate citrate lyase (ACL)
- **Ezetimibe** inhibits the intestinal absorption of cholesterol.
- **Inclisiran** limits production of PCSK9, increasing uptake of LDL-cholesterol and thereby lowering levels in blood.
- **PCSK9 inhibitors** (mAb), block degradation of LDL-c receptors, reducing circulating LDL-c.



Ezetimibe 10mg tablets	Inclisiran 184mg▼	Bempedoic Acid 210mg▼	PCSK-9 inhibitors▼
Can be prescribed across all levels of care	Check your local formulary	Check your local formulary	Specialist only Two available on the market
For primary or secondary prevention	Secondary Prevention where the LDL-c is persistently above 2.6mmol/L	Primary or Secondary Prevention	For very high risk patients with FH with/without CVD
• Monotherapy • Combination therapy	• In combination with one or more maximal tolerated lipid lowering therapies • Statin Intolerance	• In combination with Ezetimibe 10mg. • Monotherapy - not approved by NICE, but could be used when statins and ezetimibe are contraindicated/intolerance	Refer to your local guidelines and BNF
Monotherapy 15-22% LDL-c reduction	50% LDL-c reduction	• Monotherapy: 21% LDL-c. • Bempedoic Acid + Ezetimibe: 38% LDL-c reduction	50-60% LDL-c reduction
10mg daily	One injection, repeat after 3 months then 6 monthly maintenance	210mg daily	Self-administered injection every 2-4 weeks
	Awaiting long term cardiovascular outcome data (published 2026)	Awaiting long term cardiovascular outcome data	
Contraindicated in moderate to severe active liver disease Pregnancy and breastfeeding	Caution in severe impairment Pregnancy and breastfeeding	Avoid in active gout or discontinue if gout occurs Caution in severe impairment	Confirm with your local consultant
Generally well tolerated G.I symptoms	Well tolerated Injection site reactions	Gout, Anaemia,	Injection site reactions

Deprescribing



Patients aged 65 years or older who were exposed to polypharmacy, discontinuing therapy with statins while maintaining blood pressure–lowering, antidiabetic, and antiplatelet drug therapies was associated with an increased risk of fatal and nonfatal CV outcomes. This occurred in younger and older patients, men and women, patients with mild or severe clinical profiles, and irrespective of whether statins were prescribed in as primary or secondary CV prevention.

JAMA Netw Open. 2021;4(6):e2113186. doi:10.1001/jamanetworkopen.2021.13186

Primary prevention

- *For those with a life expectancy of **less than 2.5 years**, the harms of statins may outweigh the benefits*

  JAMA Intern Med. 2021;181(2):179-185. doi:10.1001/jamainternmed.2020.6084

Secondary Prevention

- *Patients aged ≥80 years remain at **highest risk** for incident and recurrent cardiovascular events and experience worst outcomes*

  American Heart Association. Circulation 2013; 128(22): 2422-2446.

- *At 6 years follow up: statin discontinuation was associated with a higher rate of occurrence of cardiovascular events compared with statin continuation among older people receiving long-term statin treatment for secondary prevention*

  JAMA Netw Open. 2021;4(12):e2136802. doi:10.1001/jamanetworkopen.2021.36802

What can we do?

- Every LDL-c reduction will reduce the patient's cardiovascular risk.
- Taking steps to ensure that everyone who would benefit from lipids optimisation is identified and offered appropriate treatment
  - Consider running a quality improvement programme within your service.
- Raise awareness as statins being first line to reduce cardiovascular events
  - Proven long term outcomes, low rate of true intolerance
- Intensifying therapy early with additional lipid lowering therapies, where statins alone have not achieved treatment targets
- Empowering patients through shared decision-making conversations to improve adherence.

Additional Resources

NHS Accelerated Access Guidelines

- Treatment Pathway https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/
- Statin Intolerance Pathway https://www.england.nhs.uk/aac/publication/statin-intolerance-pathway/
- Nice CKS https://cks.nice.org.uk/topics/lipid-modification-cvd-prevention/

Patient Decision Aids

- QRISK3 / QRISKLIFETIME https://www.qrisk.org/index.php
- GPEvidence https://gpevidence.org/
- NICE – Should I take a Statin? https://www.nice.org.uk/guidance/ng238

Further education and training:

- BJCardio E-Learning Programme https://bjcardio.co.uk/category/lipids-learning/
- HeartUK https://www.heartuk.org.uk/tackling-cholesterol-together/e-learning
- Prescqipp https://store.prescqipp.info/product/lipid-modification/
- Primary Care Cardiovascular Society https://pccsuk.org/

Questions?

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