Lipid Lowering Update

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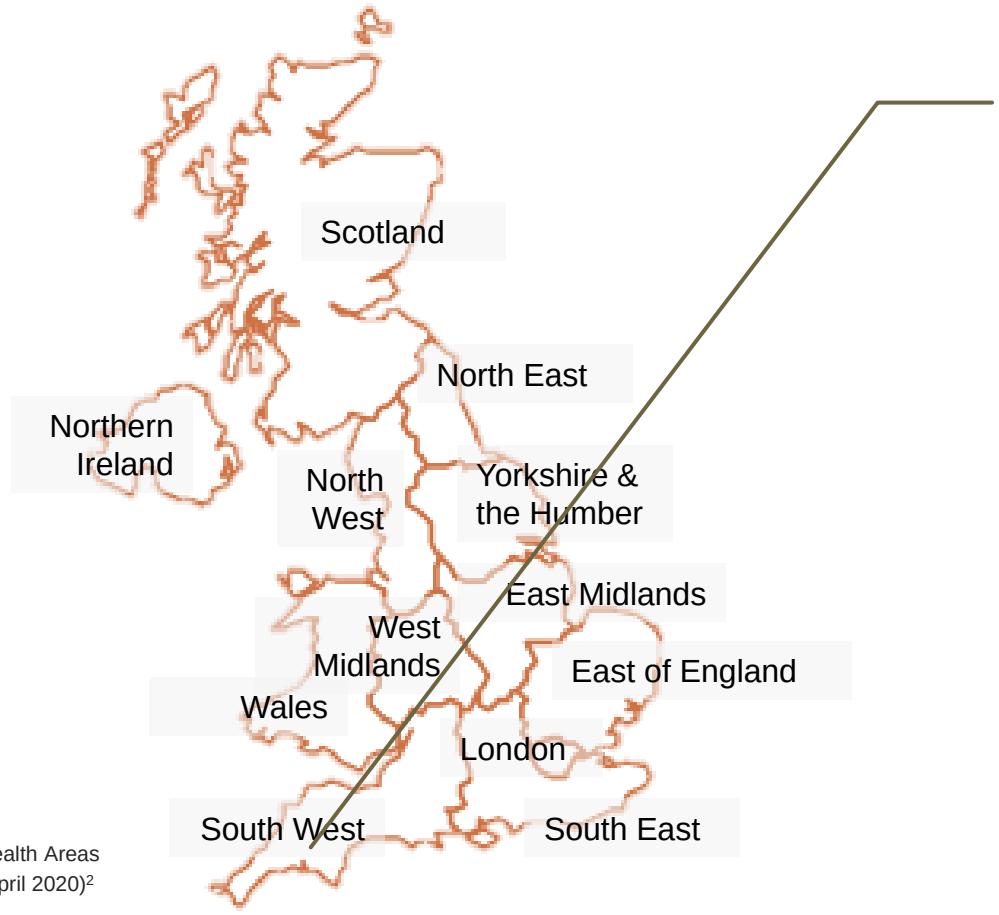
Contents

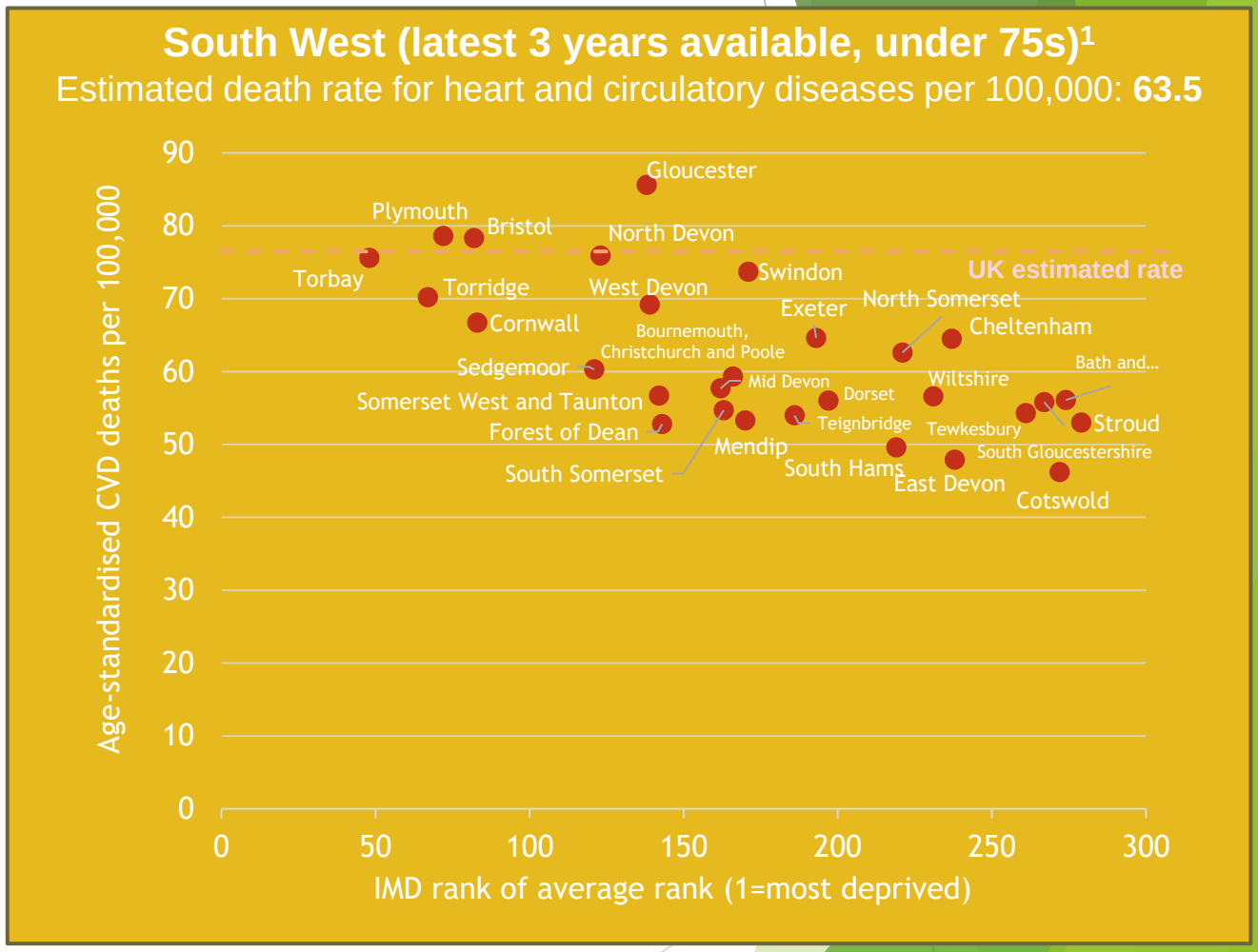
- The clinical problem
- The benefit of LDL cholesterol lowering & new targets
- Medications used to lower cholesterol and their side-effects
- New lipid lowering therapies
- When to refer to the Lipid Clinic

Areas with higher deprivation* show higher rates of mortality from CVD[1]

In the UK, estimated death rate for heart and circulatory diseases per 100,000: 76.1[1]



Health Areas (April 2020)[2]



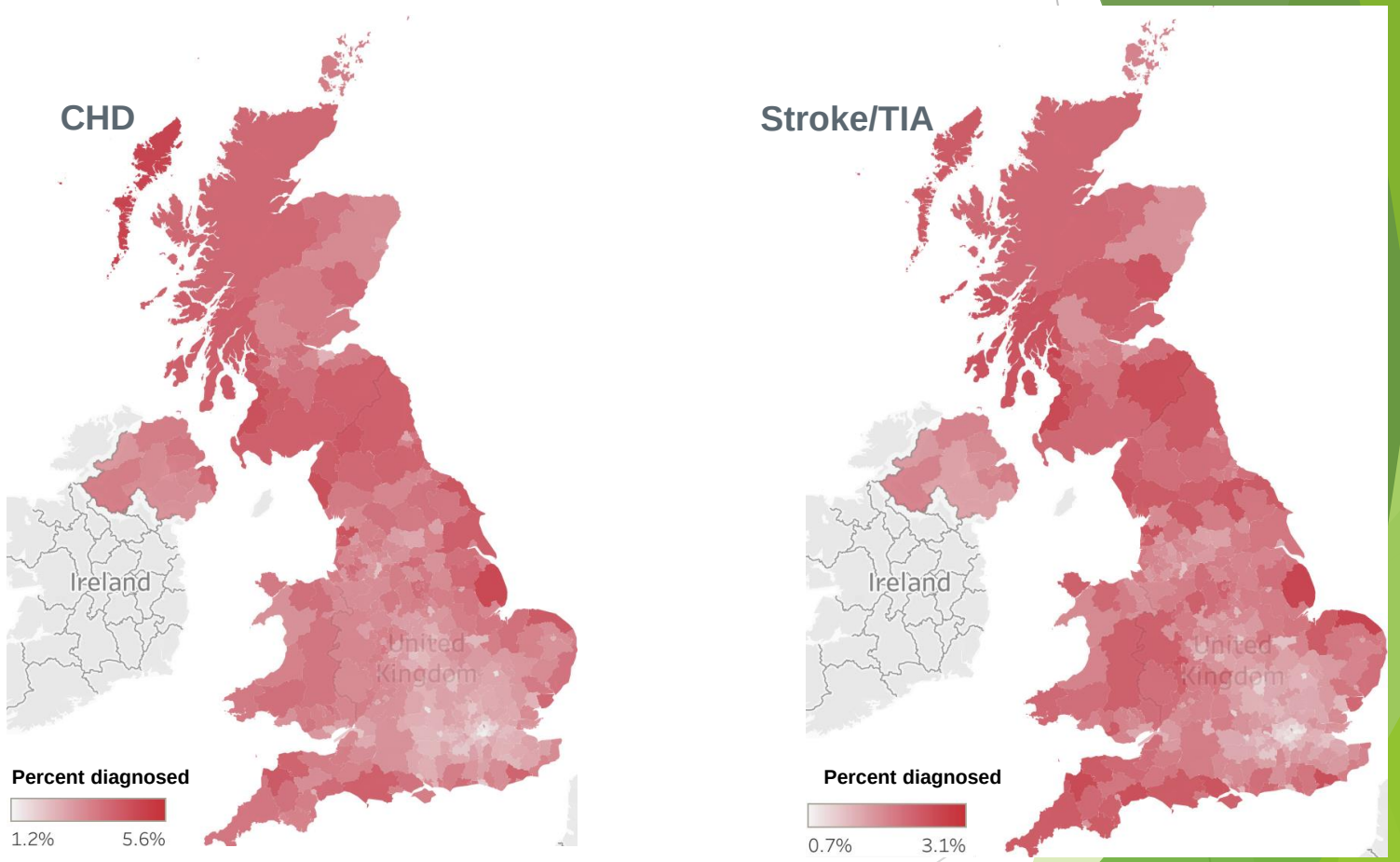
- Most recent official and health survey data are used to produce an estimate for numbers living with heart and circulatory diseases across the UK. *Per IMD, an overall measure of deprivation constructed by combining seven domains of deprivation according to their respective weights (income deprivation: 22.5%; employment deprivation: 22.5%; education, skills and training deprivation: 13.5%; health deprivation and disability; 13.5%; crime: 9.3%; barriers to housing and services: 9.3%; living environment deprivation: 9.3%).[2,3]
- CVD: Cardiovascular disease; IMD: Index of Multiple Deprivation.

- 1. British Heart Foundation. Heart and Circulatory Disease Statistics 2020. Available at https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications/cardiovascular-disease-statistics-2020. Accessed March 2021. 2. ONS. Health Areas (April 2020) Map in England and Wales. Available at https://geoportal.statistics.gov.uk/datasets/c39a892d9c1846ddbfbe7e0bd5832dea. Accessed March 2021. 3. National Statistics. English indices of deprivation 2019. Available at https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019. Accessed March 2021.

CVD is responsible for 27% of all deaths in the UK[1]

CVD leads to
1 death
every 3 minutes[1]

The diagnosed prevalence of cardiovascular related conditions varies by region (2018/2019)[2]



- CHD: Coronary heart disease; CVD: Cardiovascular disease; TIA: Transient ischaemic attack.
- 1. British Heart Foundation. CVD statistics factsheet - UK. Available at https://www.bhf.org.uk/-/media/files/research/heart-statistics/bhf-cvd-statistics-uk-factsheet.pdf?la=en&rev=0b648336c51b4e93abcf8f1bc3e5fc77&hash=2A148FB72D2BAFA8921BEFC8BAB719EC64B69185 . Accessed April 2021. 2. British Heart Foundation. Diagnosed prevalence by local authority 2018/19. Available at https://www.bhf.org.uk/what-we-do/our-research/heart-and-circulatory-diseases-in-numbers/incidence-and-prevalence-incidence-by-local-authority. Accessed April 2021.

The Clinical Problem (NICE)

- 160,000 deaths from CVD in 2015 (26% of all death in UK)
- 42,000 under age 75 died from CVD
- Death rates peaked in the 1970s
- Healthcare costs of CVD - £9 billion
- CVD cost to the UK Economy £19 billion

Elevated LDL-C is a major modifiable risk factor for ASCVD[1,2]

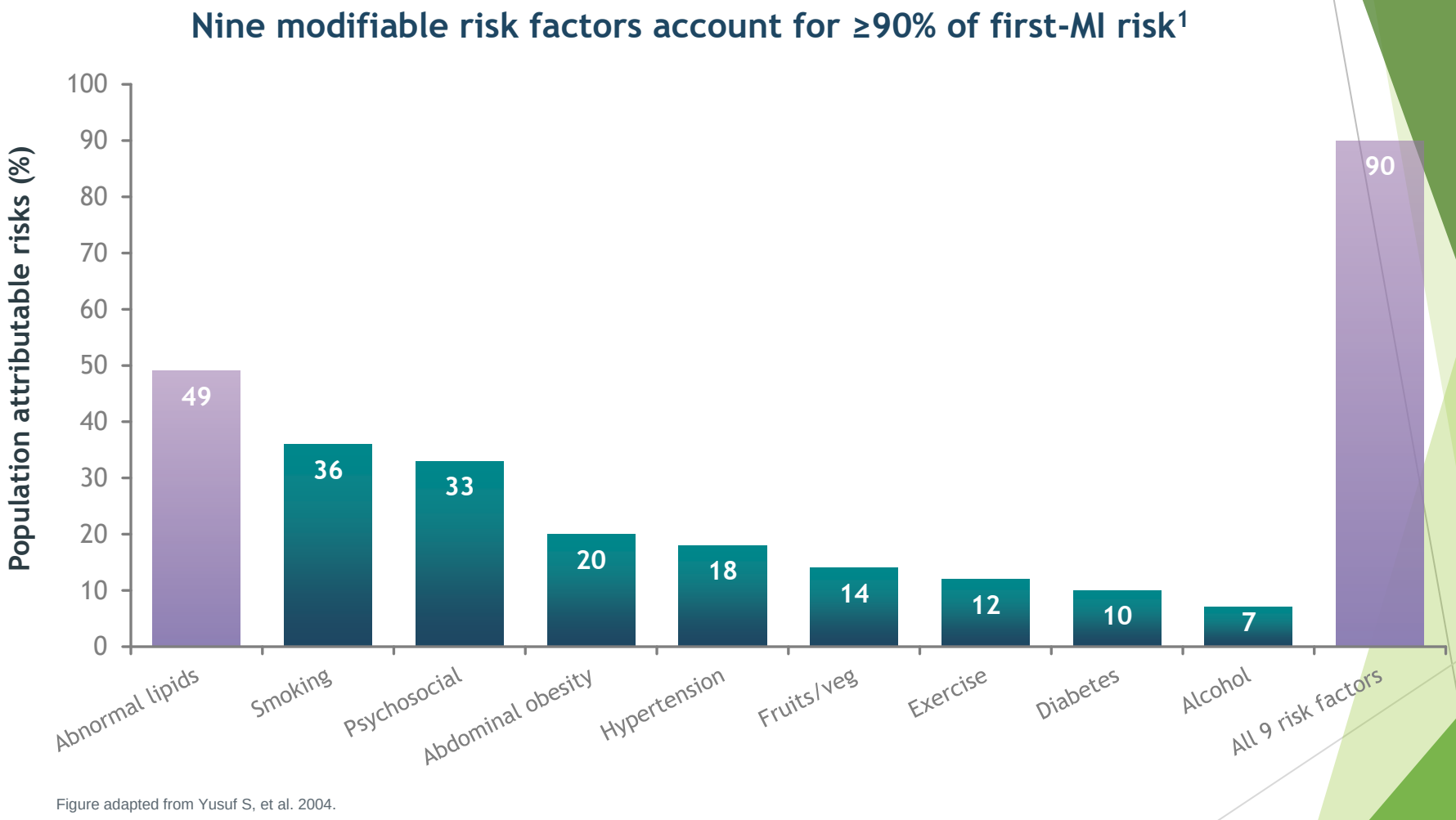
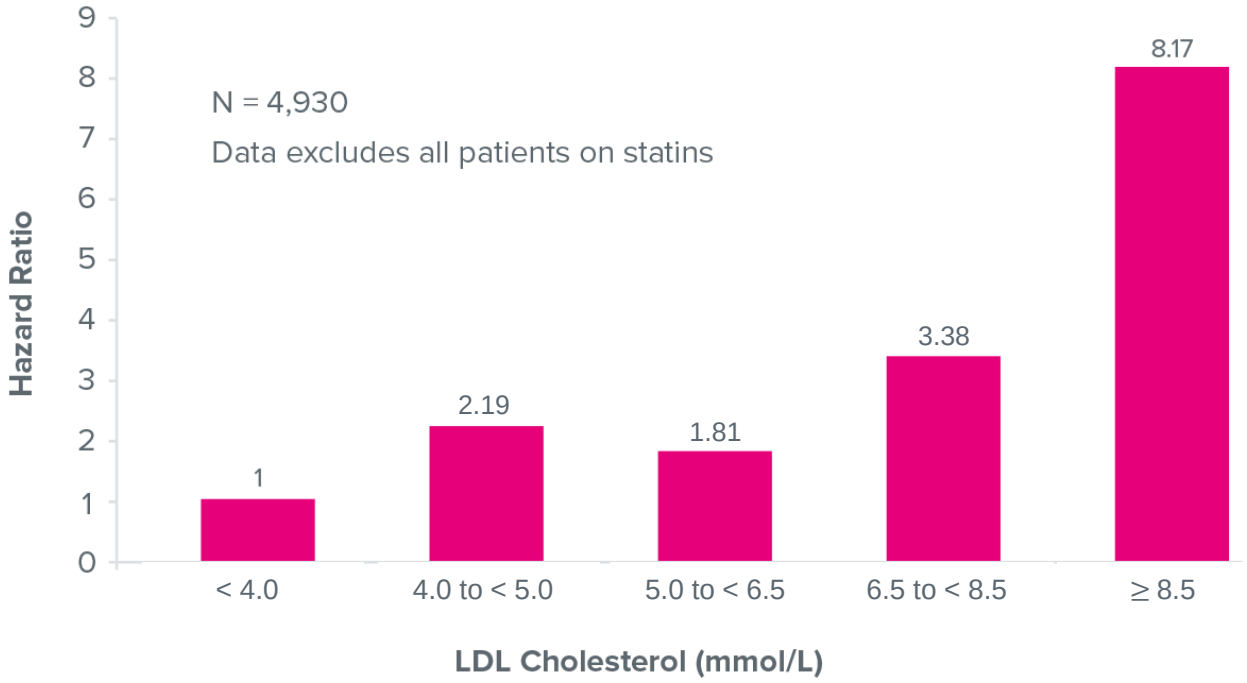


Figure adapted from Yusuf S, et al. 2004.

- ASCVD: atherosclerotic cardiovascular disease; LDL-C: low density lipoprotein cholesterol; MI: myocardial infarction; PAR: population attributable risks.
- 1. Yusuf S, et al. Lancet 2004;364:937–952; 2. ESC/EAS Guidelines for the management of dyslipidaemias. Mach F, et al. Eur Heart J 2020;41:111–188.

Tackling increased LDL-C could help us combat high rates of CVD-related mortality[1,2]

- **Overall mortality risk increases with LDL-C Level[4]**



Adapted from Séguro F, et al. 2015

Increased LDL-C levels are **a proven, direct cause of ASCVD[1-3]**

- LDL-C levels in patients with HeFH are **two- to three-fold higher** than patients without HeFH[5]

- ASCVD: Atherosclerotic cardiovascular disease, CVD: Cardiovascular disease; HeFH: Heterozygous Familial Hypercholesterolemia, LDL-C: Low-density lipoprotein cholesterol.
- 1. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1):111-188. 2. Borén J, et al. Eur Heart J. 2020; 0: 1-28. 3. Ference BA, et al. Eur Heart J. 2017; DOI: 10.1093/eurheartj/ehx450. 4. Séguro F, et al. Arch Cardiovasc Dis. 2015; 108: 511-518. 5. Krähenbühl S, et al. Drugs. 2016; 76(12): 1175-1190.

Diagnosis of FH

Total Cholesterol >7.5 mmol/L & LDL > 4.9 adults
Total Cholesterol >6.7 mmol/L & LDL > 4.0 children
Consider FH

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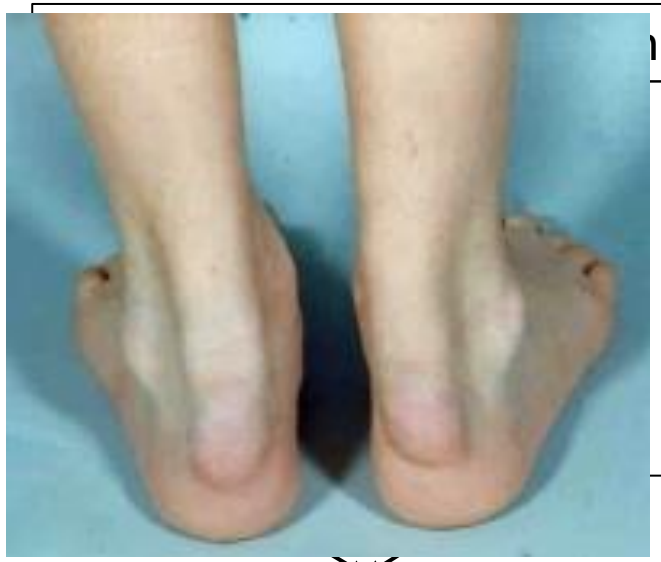
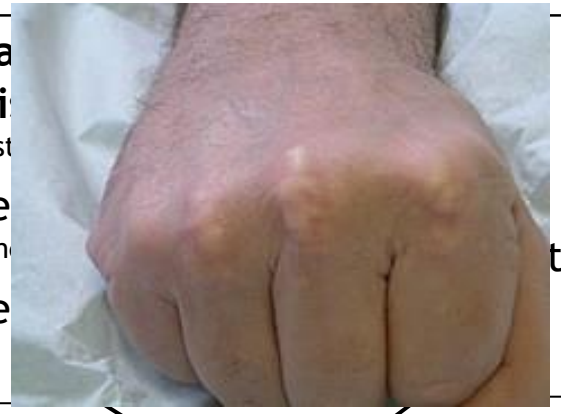
Broome Criteria





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Definite Familial Hypercholesterolaemia

Possible Familial Hypercholesterolaemia

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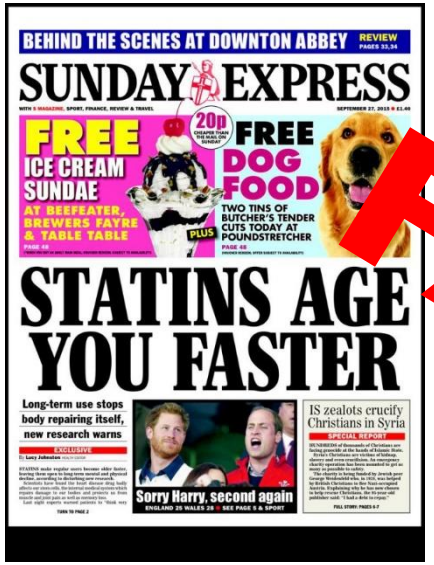
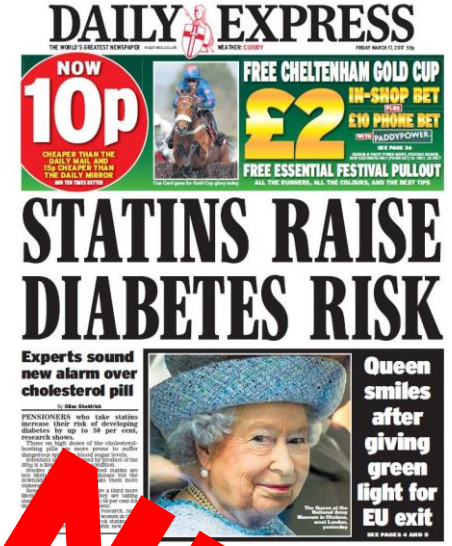
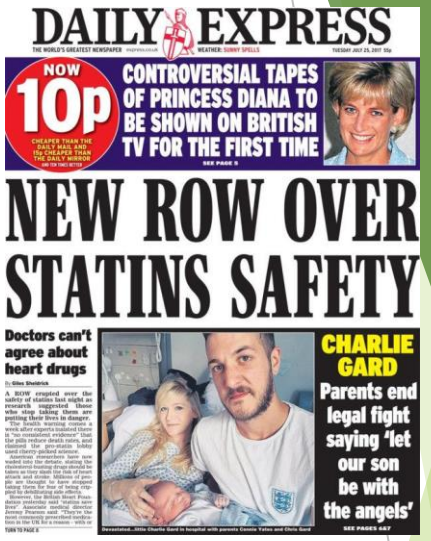
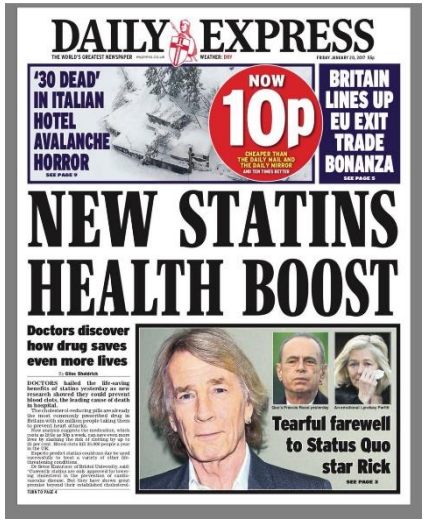
Refer All to Secondary Care

Statins









FAKE NEWS

More than 15m patients will be offered 'life-saving' statins under new NHS guidance

Life-saving statins will be offered to millions of Britons. Health chiefs are convinced the move will dramatically slash heart attacks and stroke deaths, saving thousands of lives.

By GILES SHELDRICK - DAILY EXPRESS CHIEF REPORTER
22:01, Thu, Jan 12, 2023

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December 4, 2015

To Whom My Concern:

I have been the personal physician of Mr. Donald J. Trump since 1980. His previous physician was my father, Dr. Jacob Bornstein. Over the past 39 years, I am pleased to report that Mr. Trump has had no significant medical problems. Mr. Trump has had a recent complete medical examination that showed only positive results. Actually, his blood pressure, 110/65, and laboratory test results were astonishingly excellent.

Over the past twelve months, he has lost at least fifteen pounds. Mr. Trump takes 81 mg of aspirin daily and a low dose of a statin. His PSA test score is 0.15 (very low). His physical strength and stamina are extraordinary.

Mr. Trump has suffered no form of cancer, has never had a hip, knee or shoulder replacement or any other orthopedic surgery. His only surgery was an appendectomy at age ten. His cardiovascular status is excellent. He has no history of ever using alcohol or tobacco products.

If elected, Mr. Trump, I can state unequivocally, will be the healthiest individual ever elected to the presidency.

Harold N. Bornstein, M.D., F.A.C.G.
Department of Medicine, Section of Gastroenterology
Lenox Hill Hospital, New York, NY

Review

Interpretation of the evidence for the efficacy and safety of statin therapy

Rory Collins, Christina Reith, Jonathan Emberson, Jane Armitage, Colin Baigent, Lisa Blackwell, Roger Blumenthal, John Danesh, George Davey Smith, David DeMets, Stephen Evans, Malcolm Law, Stephen MacMahon, Seth Martin, Bruce Neal, Neil Poulter, David Preiss, Paul Ridker, Ian Roberts, Anthony Rodgers, Peter Sandercock, Kenneth Schulz, Peter Sever, John Simes, Liam Smeeth, Nicholas Wald, Salim Yusuf, Richard Peto

Lancet 2016; 388: 2532–61

Summary

This Review is intended to help clinicians, patients, and the public make informed decisions about statin therapy for

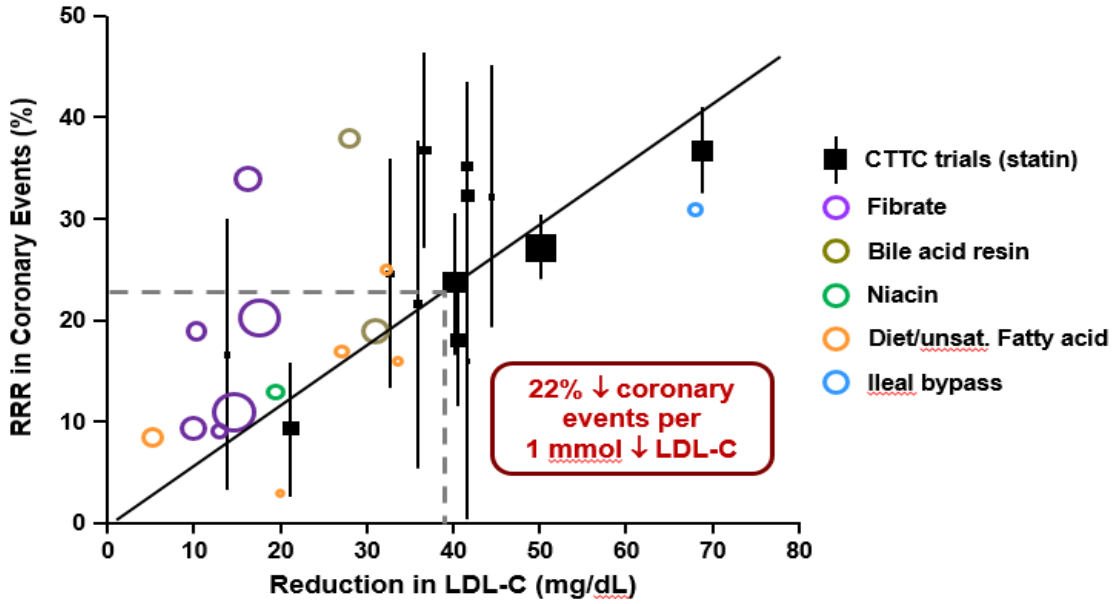
All trials (statin vs control OR more vs less statin): Proportional effects on MAJOR VASCULAR EVENTS per mmol/L reduction in LDL-C

Outcome	No. of events (% per annum) Statin/more	Control/less	RR (CI) per mmol/L LDL-C reduction
Non-fatal MI	3485 (1.0)	4593 (1.3)	0.73 (0.69 - 0.78)
CHD death	1887 (0.5)	2281 (0.6)	0.80 (0.74 - 0.87)
Any major coronary event	**5105 (1.4)**	**6512 (1.9)**	**0.76 (0.73 - 0.78)**
CABG	1453 (0.4)	1857 (0.5)	0.75 (0.69 - 0.82)
PTCA	1767 (0.5)	2283 (0.7)	0.72 (0.65 - 0.80)
Unspecified	2133 (0.6)	2667 (0.8)	0.76 (0.70 - 0.82)
Any coronary revascularisation	**5353 (1.5)**	**6807 (2.0)**	**0.75 (0.72 - 0.78)**
Ischaemic stroke	1427 (0.4)	1751 (0.5)	0.79 (0.72 - 0.87)
Haemorrhagic stroke	257 (0.1)	220 (0.1)	1.12 (0.88 - 1.43)
Unknown stroke	618 (0.2)	709 (0.2)	0.88 (0.76 - 1.01)
Any stroke	**2302 (0.6)**	**2680 (0.8)**	**0.84 (0.79 - 0.89)**
Any major vascular event	**10973 (3.2)**	**13350 (4.0)**	**0.78 (0.76 - 0.80)**

Lancet 2010; 376: 1670-81

CTT Collaboration

LDL Reduction Lowers CV Risk

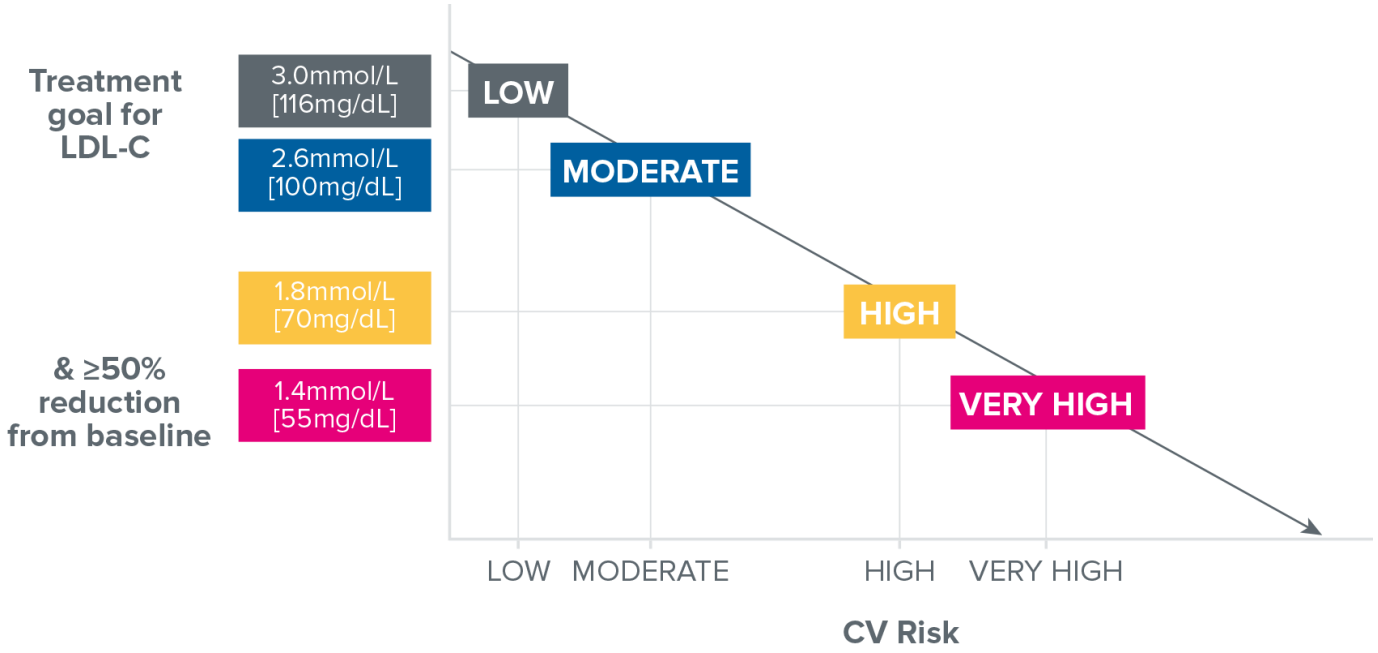


Data from studies of non-statin lipid-lowering medications superimposed upon data from the Cholesterol Treatment Trialist's 2005 meta-analysis suggest that **reduction of coronary event risk due to reduction of LDL-C is independent of method**

GUIDELINES

The ESC/EAS Guidelines recommend intensive reduction of LDL-C in uncontrolled patients to reduce CV risk[1]

Recommendations across CV risk categories[1]



Adapted from the ESC/EAS guidelines, 2019

- The updated ESC/EAS Guidelines recommend an LDL-C reduction of ≥50% from baseline and LDL-C goals of <1.8 mmol/L and <1.4 mmol/L in high-risk and very high-risk patients, respectively[1]

The ESC/EAS Guidelines recommend adding a non-statin LLT to a maximally tolerated statin therapy in patients who cannot tolerate the recommended intensity of a statin because of adverse effects or have not achieved their lipid goal[1]

- CV: cardiovascular; EAS: European Atherosclerosis Society, ESC: European Society of Cardiology, LDL-C: Low-density lipoprotein cholesterol, LLT: Lipid lowering therapy.

- 1. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2020; 41(1): 111-188.

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

ACCELERATED ACCESS COLLABORATIVE

NHS

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 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)

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate offer statin treatment.

Atorvastatin 20mg daily

- 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 daily.
  - 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 *'Extent of lipid lowering with available therapies'*)
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value after 3 months consider adding Ezetimibe 10mg daily (NICE TA385)
- If statin treatment is contraindicated or not tolerated;
  - See AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here)
  - Ezetimibe 10mg monotherapy may be considered. Assess response after 3 months.
  - Ezetimibe 10mg/bempedoic acid 180 mg combination may be considered when ezetimibe alone does not control non-HDL-C/LDL-C well enough (NICE TA694).

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 with 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 CHD, angina, Acute Coronary Syndrome (MI or unstable angina), 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.
Prescribe a high intensity statin:

Atorvastatin 80mg daily

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*, consider target non-HDL-C < 2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/L) as recommended by Joint British Societies (JBS3).
  **this scenario is not currently covered by NICE CG181. NICE will consider this as part of the guideline update with publication currently expected September 2023*
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*)

If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 3 months confirm statin adherence, then consider the following options based on shared decision making* with the patient

If recommended statin treatment is contraindicated or not tolerated - follow AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here).

If statin intolerance is confirmed, consider:

- **Ezetimibe 10mg** monotherapy. Assess response after 3 months (TA385)
- **Ezetimibe 10mg/bempedoic acid 180 mg** combination when ezetimibe alone does not control non-HDL-C sufficiently. (NICE TA694)

If non HDL-C remains > 2.5mmol/L despite other lipid lowering therapies consider Injectable therapies - arrange a fasting blood test and assess eligibility criteria (TA393/394, TA733)

Ezetimibe 10mg daily (NICE TA385). Reassess after three months. If non-HDL-C remains > 2.5mmol/L; consider **injectable therapies** arrange a fasting blood test and assess eligibility

Injectable therapies**

If non-HDL-C > 2.5mmol/L; Arrange fasting blood test to measure LDL-C to assess eligibility:

- **Inclisiran** - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy (TA733)

OR

- **PCSK9i** - see overleaf for LDL-C thresholds. (TA393/4)

If eligibility criteria not met, consider **ezetimibe 10mg daily** (if not previously considered)

* See overleaf for information to support shared decision making

** Inclisiran and PCSK9i should not be prescribed concurrently

Additional CV risk reduction considerations - check fasting triglycerides levels and consider icosapent ethyl. See triglycerides section overleaf.

MANAGEMENT

This guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. If 40% reduction of non-HDL-C not achieved, offer high intensity statins. Discuss with people who are stable on a low- or medium-intensity statin the likely benefits and potential risk of side effects if changed to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.

Ezetimibe, alirocumab, evolocumab or inclisiran can be added when patients' LDL-C levels are not lowered enough with the maximally tolerated dose of statins. Bempedoic acid with ezetimibe is an option when statins are contraindicated or not tolerated, and when ezetimibe alone does not control LDL-C well enough. Do not offer a fibrate, nicotinic acid, bile acid binder or omega-3 fatty acids alone or in combination with statin, for the prevention of CVD (check NICE CG181 and TA805 for exceptions).

PRIMARY PREVENTION RISK ASSESSMENT

QRISK3 is the current version of the QRISK calculator. www.qrisk.org/three

- Do not use this risk assessment tool for people with established CVD or those who are at high risk of developing CVD because of FH or other inherited disorders of lipid metabolism.
- Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes, or eGFR less than 60 mL/min/1.73 m² and/or albuminuria.
- Consider people aged ≥ 85 at increased risk of CVD because of age alone particularly people who smoke or have raised BP.

Additional Risk Factors

Note, standard CVD risk scores including QRISK may underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include the following groups of people;

- severe obesity (BMI>40kg/m²) increases CVD risk
- treated for HIV
- serious mental health problems
- taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
- autoimmune disorders such as SLE, and other systemic inflammatory disorders
- non-diabetic hyperglycaemia
- significant hypertriglyceridaemia (fasting triglycerides 4.5-9.9mmol/L)
- recent risk factor changes e.g. quit smoking, BP or lipid treatment

Consider socio-economic status as an additional factor contributing to CVD risk.

If QRISK < 10% over the next 10 years - Give lifestyle advice and ensure regular review of CVD risk in line with guidance.

SPECIAL PATIENT POPULATIONS

Type 1 Diabetes

While NICE recommends offering statins to patients with Type 1 diabetes as detailed in the algorithm, it also states to consider statins in all adults with type 1 diabetes.

Chronic Kidney Disease

Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD (eGFR less than 60 mL/min/1.73m² and/or albuminuria)

Increase the dose if a greater than 40% reduction in non-HDL-C is not achieved and eGFR is 30 mL/min/1.73m² or more.

Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m²

ABBREVIATIONS

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CHD: coronary heart disease
CKD: chronic kidney disease
CVD: cardiovascular disease
FH: familial hypercholesterolaemia
LDL-C: low density lipoprotein cholesterol
non-HDL-C: non-high density lipoprotein cholesterol
PCSK9i: proprotein convertase subtilisin kexin 9 monoclonal antibody inhibitor
SLE: systemic lupus erythematosus
SPC: summary of product characteristics
TC: total cholesterol

EXTENT OF LIPID LOWERING WITH AVAILABLE THERAPIES

Approximate reduction in LDL-C					
Statin 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%	
Atorvastatin + Ezetimibe 10mg		52%	54%	57%	61%

Low intensity statins will produce an LDL-C reduction of 20-30%

Medium intensity statins will produce an LDL-C reduction of 31-40%

High intensity statins will produce an LDL-C reduction above 40%

Simvastatin 80mg is not recommended due to risk of muscle toxicity

- **Rosuvastatin** may be used as an alternative to atorvastatin if compatible with other drug therapy. Some people may need a lower starting dose (see BNF).
- Low/medium intensity statins should only be used if intolerance or drug interactions.
- **Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C or LDL-C than doubling the dose of the statin.
- **PCSK9i** (NICE TA393, TA394) alone or in combination with statins or ezetimibe produce an additional LDL-C reduction of approximately 50% (range 25-70%).
- **Bempedoic acid** when combined with ezetimibe (TA694) produces an additional LDL-C reduction of approximately 28% (range 22-33%) but no clinical outcome evidence is currently available.
- **Inclisiran** (TA733) alone or in combination with statins or ezetimibe produces an additional LDL-C reduction of approximately 50% (range 48-52%) but no clinical outcome evidence is currently available.

MONITORING

Baseline Measurements

In addition to full lipid profile, measure renal, thyroid and liver profiles (including albumin) and HbA1c to exclude secondary causes and co-morbidities.
Measure baseline liver transaminase (ALT or AST) before starting a statin.
Measure CK if unexplained muscle pain before starting a statin.
CK should not be measured routinely especially if a patient is asymptomatic.

	Primary Prevention		Secondary prevention	
	Lipid Profile	ALT or AST	Lipid Profile	ALT or AST
Baseline	✓	✓	✓	✓
3 months	✓	✓	✓	✓
6-9months	If <40% non-HDL-C reduction, up titration required. Repeat full lipid profile and ALT or AST within 3 months of each up-titration of statin dose or addition of ezetimibe as required			
12 months	✓	✓	✓	✓
Yearly	✓*		✓*	

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, lifestyle modification and address CVD risk factors.

Consider an annual non-fasting **full lipid profile to inform the discussion around effectiveness of lipid lowering therapy and any medicines non-adherence.*

Monitoring

Repeat full lipid profile is non-fasting.
Measure liver transaminase within 3 months of starting treatment and then within 3 months of every additional up titration and then again at 12 months, but not again unless clinically indicated.

If ALT or AST are greater than 3 times the upper limit of normal then do not initiate a statin or discontinue statin therapy already prescribed and repeat the LFTs in a month.

If ALT or AST are elevated but are less than 3 times the upper limit of normal then:

- Continue the statin and repeat in a month.
- If they remain elevated but are less than 3 times the upper limit of normal then continue statin and repeat again in 6 months.

TITRATION THRESHOLD / TARGETS

	NICE titration threshold	JBS3
Primary prevention Secondary Prevention	Intensify lipid lowering therapy if non-HDL-C reduction from baseline is less than 40%	non-HDL-C <2.5mmol/L (LDL-C <1.8mmol/L)
FH	Optimise lipid lowering therapy to achieve at least 50% reduction in LDL-C (or non-HDL-C.)	

If baseline cholesterol is unknown in the setting of secondary prevention use the use Joint British Societies' JBS3 consensus recommendation.
Non-HDL-C = TC minus HDL-C
LDL-C = non-HDL-C minus (Fasting triglycerides[a]/2.2)
[a] valid only when fasting triglycerides are less than 4.5 mmol/L

SPECIALIST SERVICES

Scope of specialist service available locally may include; lipid clinic, PCSK9i clinic (offering initiation and subsequent follow up), FH genetic diagnosis and cascade testing, lipoprotein apheresis service. NICE eligibility criteria for PCSK9i and fasting LDL-C thresholds are summarised below.

NICE TA393 Alirocumab NICE TA394 Evolocumab	Without CVD	With CVD	
		High risk [1]	Very high risk [2]
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL C > 4.0 mmoL/L	LDL C > 3.5 mmoL/L
Primary heterozygous-FH	LDL C > 5.0 mmoL/L	LDL C > 3.5 mmoL/L	

[1] History of any of the following: ACS; coronary or other arterial revascularisation procedures; CHD, ischaemic stroke; PAD. [2] Recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).

Bempedoic acid/ezetimibe and inclisiran are available in primary care and do not require initiation by specialist services.' PCSK9i may be available for prescribing in primary care: see local initiation pathways.

TRIGLYCERIDES

Triglyceride concentration	Action
Greater than 20mmol/L	**Refer to lipid clinic for urgent specialist review** if not a result of excess alcohol or poor glycaemic control. At risk of acute pancreatitis.
10 - 20mmol/L	Repeat the TG measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and review for potential secondary causes of hyperlipidaemia. Seek specialist advice if the TG concentration remains > 10mmol/litre. At risk of acute pancreatitis
4.5 - 9.9mmol/L	If non-fasting triglycerides are greater than 4.5mmol/L, repeat with a fasting TG measurement Be aware that the CVD risk may be underestimated by risk assessment tools, optimise the management of other CVD risk factors present and seek specialist advice if non-HDL-C concentration is > 7.5 mmol/litre.

Icosapent ethyl (TA805)

- Check fasting triglycerides levels.
- Manage secondary causes of hypertriglyceridaemia.
- Consider icosapent ethyl (TA805) if patient has established cardiovascular disease (secondary prevention) **and**
  - on statins and fasting TG ≥ 1.7mmol/L and LDL-C* between 1.04‡ and ≤2.6mmol/L
- See table above and refer as appropriate.

* LDL-C cannot be calculated using Friedewald's formula if TG >4.5. Discuss with your lab. Consider using an alternative equation (eg Sampson, doi: 10.1001/jamacardio.2020.0013) or beta-quantification.
‡ labs don't report calculated LDL-C beyond one decimal point

STATIN INTOLERANCE

Statin intolerance is defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in adherence to therapy being compromised.

For people who are intolerant of the recommended statin treatment see the NHSE AAC statin intolerance algorithm, available on the NHSE AAC page (Click here)

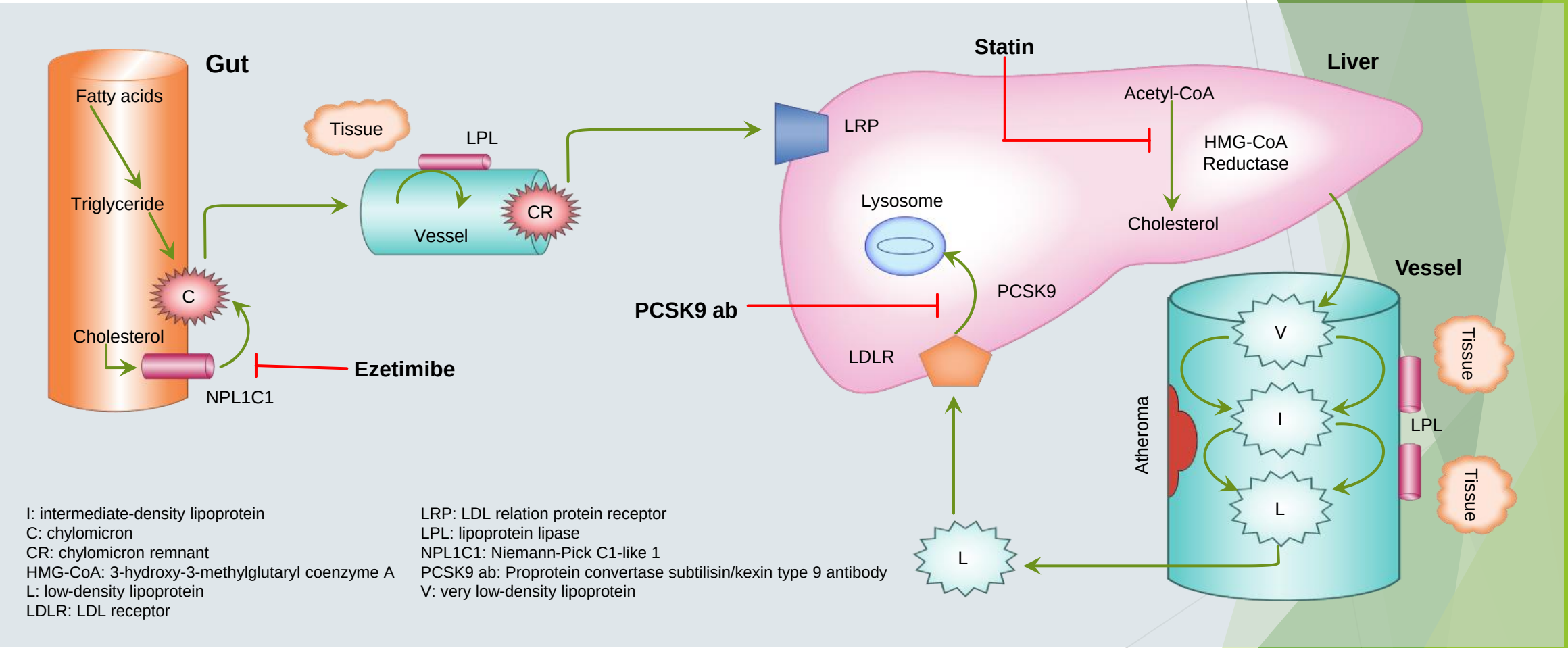
References:
JBS3. 2014. www.jbs3risk.com/pages/6.htm
Kirsten *et al.* 2005. Hospital Pharmacy 40(8):687-692
Navarese *et al.* 2015. Annals of internal medicine 163(1):40-51
Soon Jun Hong *et al.* 2018. Clinical therapeutics 40(2): 226-241.e4
NICE 2016. TA385 www.nice.org.uk/guidance/ta385
NICE 2016. TA393 www.nice.org.uk/guidance/TA393
NICE 2016. TA394 www.nice.org.uk/guidance/TA394
NICE 2014. CG181 www.nice.org.uk/guidance/CG181
NICE 2008. CG71 www.nice.org.uk/guidance/cg71
NICE 2021. TA694 www.nice.org.uk/guidance/TA694
NICE 2021. TA733 www.nice.org.uk/guidance/TA733
NICE 2022. TA805 www.nice.org.uk/guidance/ta805

Authors: Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup.

Nov 2022. Review date: Nov 2023.

NICE confirmed that its guidance is accurately represented, Nov 2022.

Numerous targets have been explored to lower LDL-C[1]



- Image used with permission.
- LDL-C: Low-density lipoprotein cholesterol.
- 1. Ryan A, et al. BMJ. 2018; 360: k946.

Lipid Lowering Therapies

	Reduction in LDL Cholesterol							
Dose mg/day	**5**	**10**	**20**	**40**	**80**	**267**	**180**	
Fluvastatin	-	-	21%	27%	33%			
Pravastatin	-	20%	24%	29%	-			
Simvastatin	-	27%	32%	37%	42%			
Atorvastatin	-	37%	43%	49%	55%			
Rosuvastatin	38%	43%	48%	53%	-			
Ezetimibe		18%						
Fenofibrate						20%		
Bempedoic Acid							17%	
PCSK9 Inhibitors								55%

Ezetimibe

- MOA – Reduces GI absorption of cholesterol
- Inhibits the Niemann-Pick C1-like 1 (NPC1L1) protein
- Reduces serum cholesterol by 18%
- Side –effects: headache, GI upset, muscle ache and deranged LFTs.

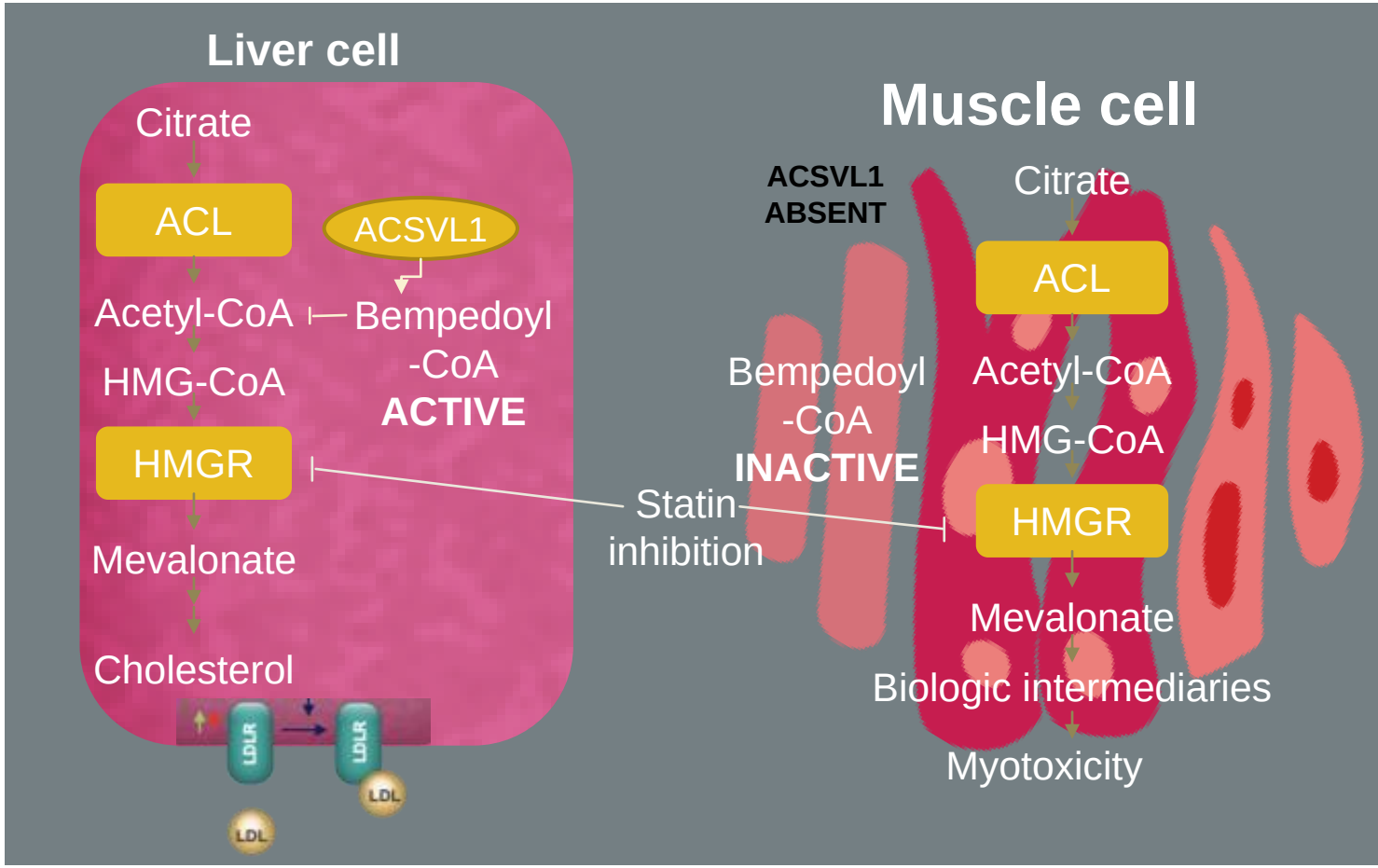
Fibrates

- MOA – activate PPARα (peroxisome proliferator-activated receptors α)
  - Transcription factor that activates lipid metabolism
- Reduces triglycerides and LDL (less), increases HDL
- Side-effects: muscle ache, rarely acute pancreatitis

New Therapies

- Anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
- Bempedoic Acid
- Inclisiran (PCSK9i with a different MOA)
- Icosapent Ethyl (Vazkepa)

The mechanism of action of bempedoic acid is complementary yet distinct from statins[1]



- Citrate is converted into cholesterol in a series of reactions in liver and muscle cells[1]
- Bempedoic acid is a pro-drug and requires activation by ACSVL1; this is expressed primarily in the liver and not in skeletal muscle[2]
- Bempedoyl-CoA, activated bempedoic acid, inhibits ACL and cholesterol synthesis (upstream of the statin target) thereby lowering LDL-C levels in the blood via upregulation of LDL receptors[1]
- Due to this novel mechanism of action, bempedoic acid is not activated in the skeletal muscle[1,2]

- Adapted from Pinkosky SL, et al. 2016.
- ACL: ATP-citrate lyase; ACSVL1: Very long-chain acyl-CoA synthetase-1; ATP: Adenosine triphosphate; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; HMGR: 3-hydroxy-3-methylglutarate-CoA reductase; LDL: Low-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein receptor; TCA: Tricarboxylic acid.
- 1. Pinkosky SL, et al. Nat Commun. 2016; 7: 13457. 2. NILEMDO®. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/11743. Accessed March 2021.

NICE Technology Appraisal Guidance [TA694] April 2021[1]

Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia[1]

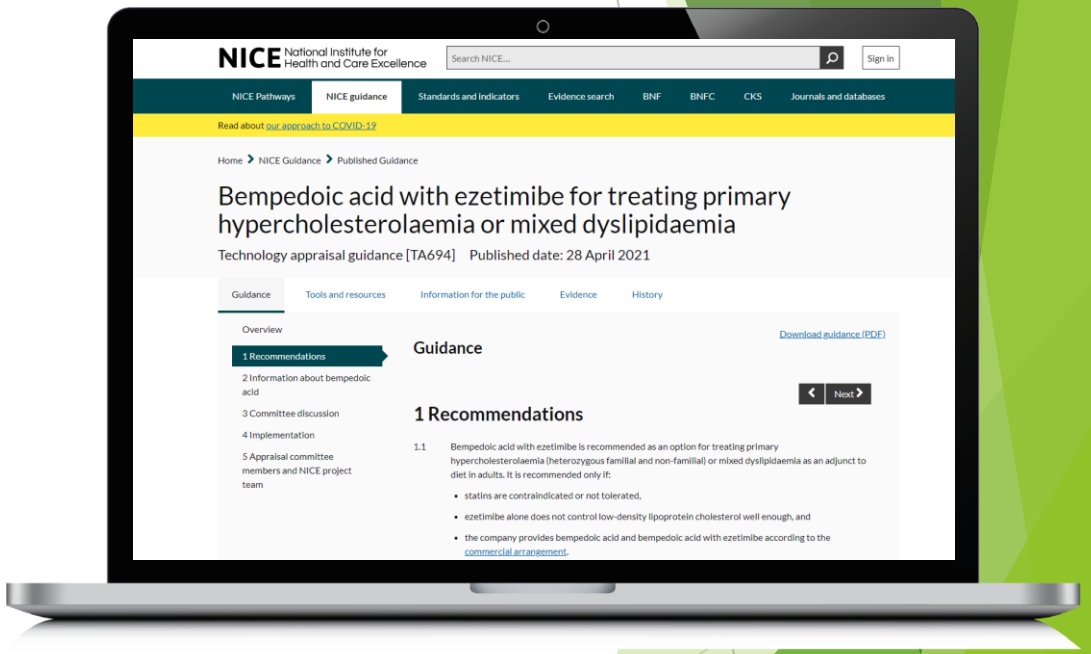
1 Recommendations

1.1 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 (see section 2).

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

1.2 This recommendation is not intended to affect treatment with bempedoic acid with ezetimibe that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.



NICE: National institute for health and care excellence.

1. NICE. Bempedoic acid for treating primary hypercholesterolaemia or mixed dyslipidaemia [TA694]. Available at www.nice.org.uk/guidance/ta694. Accessed April 2021.

NILEMDO® and NUSTENDI®

NILEMDO® (bempedoic acid)

In the clinical trial programme, NILEMDO® demonstrated a:

17–28% LDL-C REDUCTION
(placebo-corrected) from baseline at 12 weeks, depending on risk factors and concomitant medicine*[1-4]

- Most commonly reported AEs during pivotal trials were hyperuricaemia (3.8%), pain in extremity (3.1%) and anaemia (2.5%)†[6]

NUSTENDI® (bempedoic acid and ezetimibe)

NUSTENDI® demonstrated a:

38% LDL-C REDUCTION
(placebo-corrected) from baseline at 12 weeks[5]

- Most commonly reported AEs during pivotal trials were hyperuricaemia (4.7%) and constipation (4.7%) †[7]

Gout was reported in 1.4% of patients treated with bempedoic acid and 0.4% treated with placebo†[6,7]

- *Placebo-corrected LDL-C reductions in pivotal NILEMDO® studies: CLEAR Harmony, 18% (NILEMDO®: n=1,488; placebo: n=742); CLEAR Wisdom, 17% (NILEMDO®: n=522; placebo: n=257); CLEAR Serenity, 21% (NILEMDO®: n=234; placebo: n=111); CLEAR Tranquility, 28% (NILEMDO®: n=181; placebo: n=88). All p<0.001 for NILEMDO® vs placebo. CLEAR Harmony and CLEAR Wisdom included patients with ASCVD, HeFH or both, taking maximally tolerated statins (which could be no statin) +/- other LLT. CLEAR Serenity included primary and secondary prevention patients with statin intolerance taking very-low dose statin, non-statin LLT, or no LLT. CLEAR Tranquility included primary and secondary prevention patients with statin intolerance taking ezetimibe with low dose, very-low dose or no statin +/- other non-statin LLT.[1-4]
  **p<0.001 for NUSTENDI® vs placebo. Study 053 included patients with ASCVD, HeFH or multiple CVD risk factors, taking maximally tolerated statin therapy (which could be no statin).[5]
- AE: Adverse event; LDL-C: Low-density lipoprotein cholesterol.
- 1. Goldberg AC, et al. JAMA. 2019; 322: 1780-1788. 2. Laufs U, et al. J Am Heart Assoc. 2019; 8: e011662. 3. Ray KK, et al. N Engl J Med. 2019; 380: 1022-1032. 4. Ballantyne CM, et al. Atherosclerosis. 2018; 277: 195-203. 5. Ballantyne CM, et al. Eur J Prev Cardiol. 2020; 27(6): 593-603. 6. NILEMDO®. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/11743. Accessed March 2021. 7. NUSTENDI®. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/11744. Accessed March 2021.

In the clinical trial programme, NILEMDO® and NUSTENDI® were generally well tolerated[1,2]

NILEMDO (bempedoic acid)

Most commonly reported AEs during pivotal trials were:[1]

- Hyperuricaemia (3.8%)
- Pain in extremity (3.1%)
- Anaemia (2.5%)

NUSTENDI (bempedoic acid and ezetimibe)

Most commonly reported AEs during pivotal trials were:[1]

- Hyperuricaemia (4.7%)
- Constipation (4.7%)

AE: Adverse event.

1. NILEMDO®. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/11743/smpc#gref. Accessed March 2021. 2. NUSTENDI®. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/11744/smpc#gref. Accessed March 2021.

New Therapies – PCSK9 Inhibitors

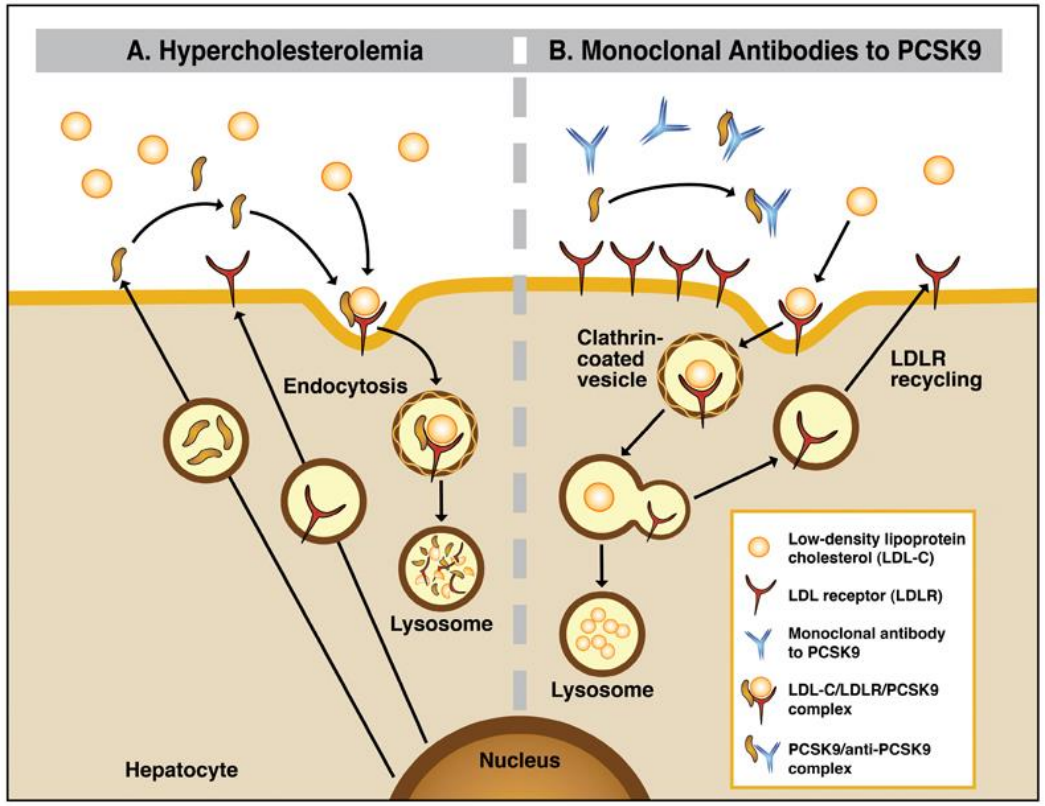
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
- 2 Available in UK Evolocumab (Repatha) & Alirocumab (Praluent)
- Monoclonal antibodies, sc injection, 2 or 4 weekly

NICE - PCSK9 Inhibitors

- Evolocumab and alirocumab can be used if the LDL remains persistently above the following thresholds despite maximum tolerated treatment:

	Without CVD	With CVD	
		High risk of CVD[1]	Very high risk of CVD[2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

PCSK9 Inhibitors



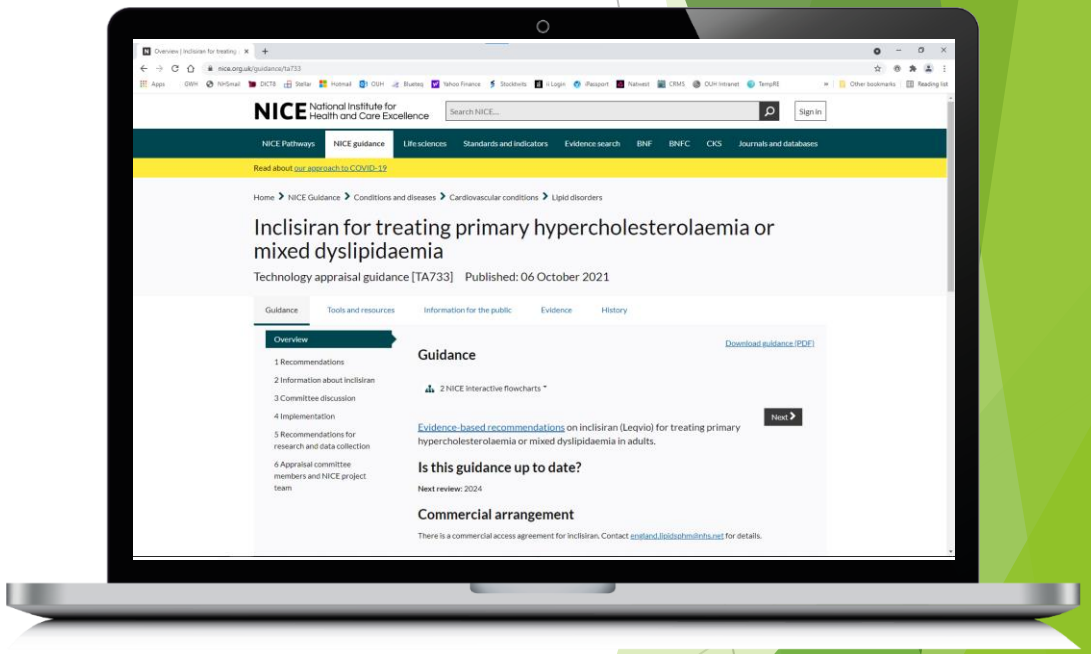
NICE Technology Appraisal Guidance [TA733] Ocotober 2021[1]

Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia[1]

1 Recommendations

1.1 Inclisiran 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:

- there is a history of any of the following cardiovascular events:
  - acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
  - coronary or other arterial revascularisation procedures
  - coronary heart disease
  - ischaemic stroke or
  - peripheral arterial disease, and
- low-density lipoprotein cholesterol (LDL-C) concentrations are persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, that is:
  - maximum tolerated statins with or without other lipid-lowering therapies or,
  - other lipid-lowering therapies when statins are not tolerated or are contraindicated, and
- the company provides inclisiran according to the commercial arrangement.



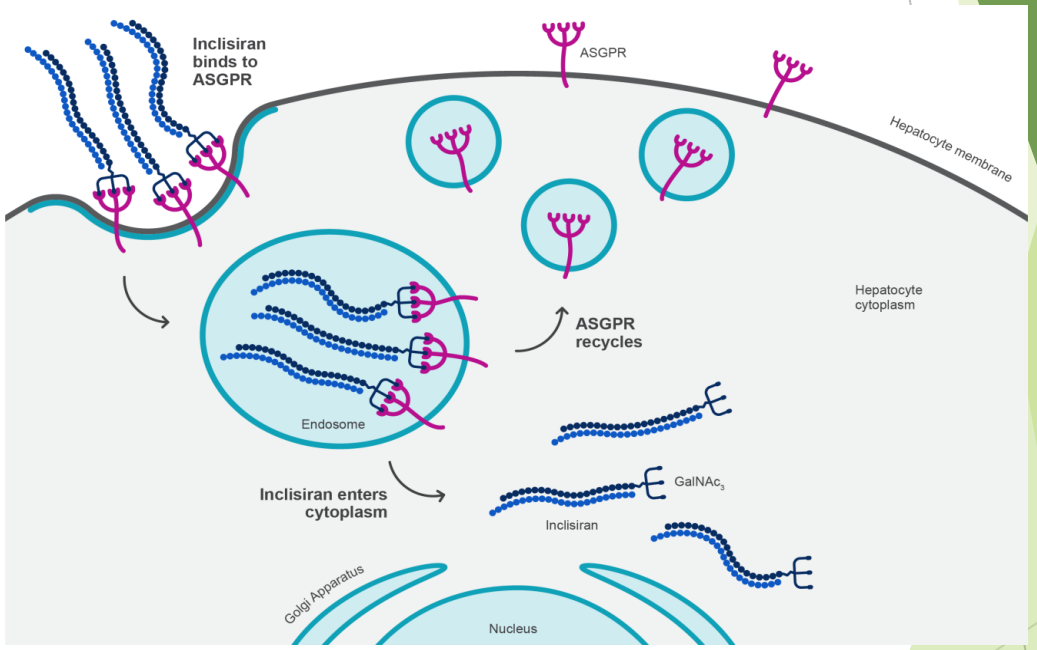
- NICE: National institute for health and care excellence.

1. NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia Technology appraisal guidance [TA733]Published: 06 October 2021.

GalNAc-siRNA conjugates facilitate rapid hepatic uptake

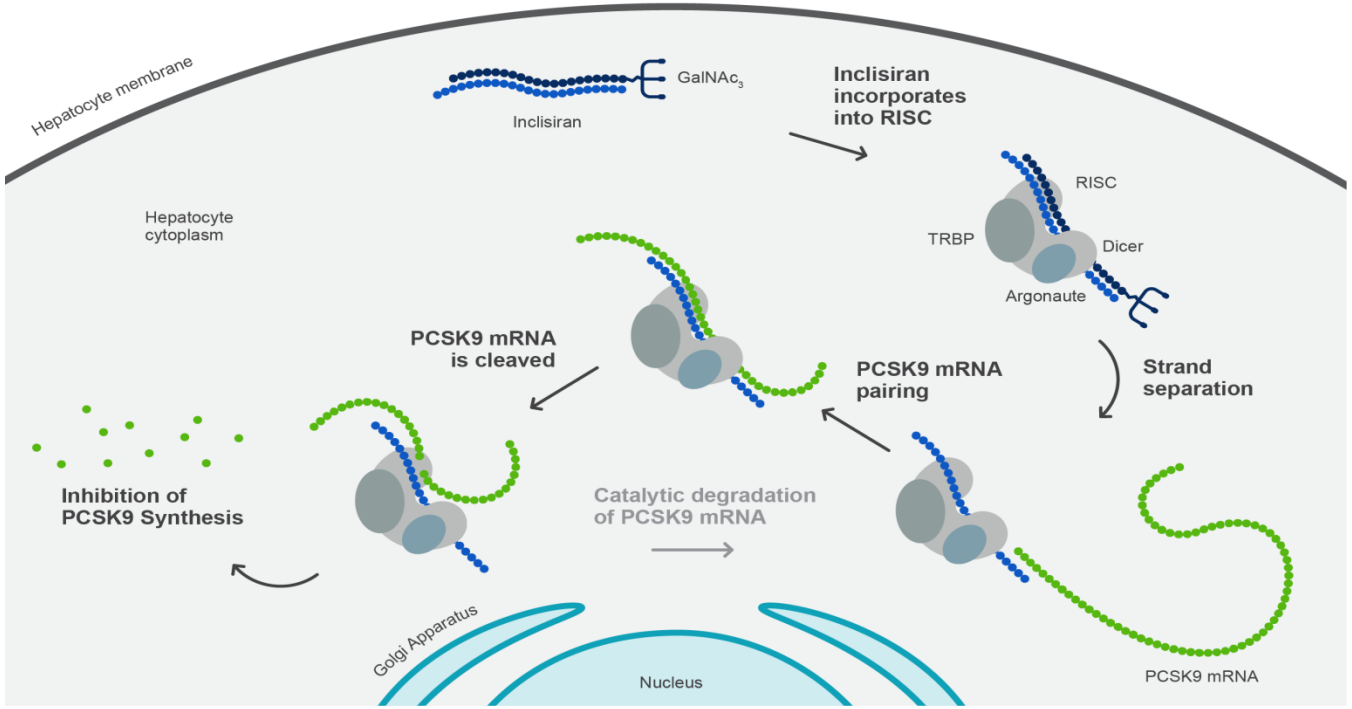
Background

- Inclisiran:
  - siRNA conjugated to N-acetylgalactosamine
  - Subcutaneous administration
  - Targeted delivery to hepatocytes
  - Third generation with enhanced stablilisation chemistry
- **Asialoglycoprotein receptor (ASGPR):**
  - Highly expressed in hepatocytes only
  - High rate of uptake



Small interfering RNA (siRNA) targeted to PCSK9

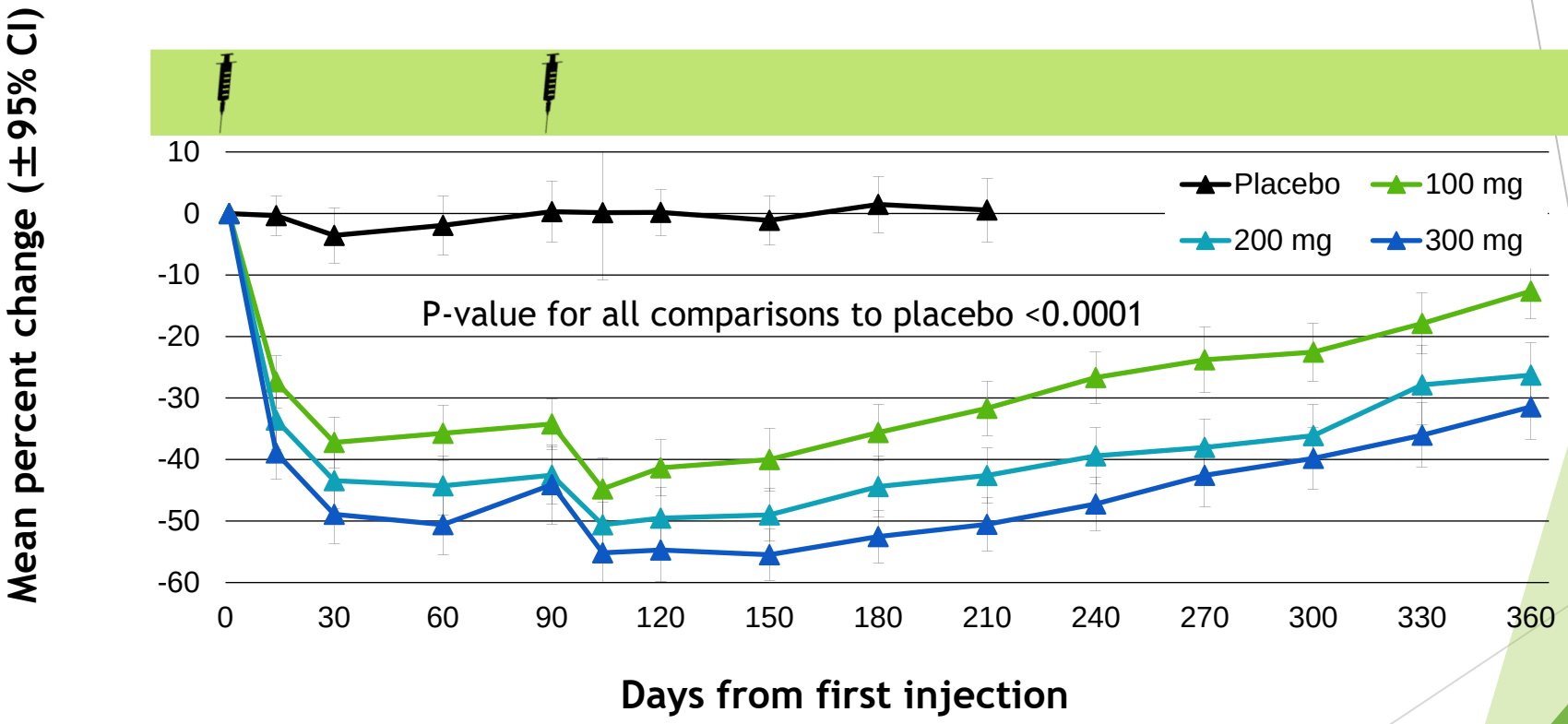
Mechanism of action



RISC: RNA Induced Silencing Complex
GalNAc: N-acetylgalactosamine
mRNA: messenger RNA

Whitehead et al. *Nat Rev Drug Discov* 2009;8:129-36

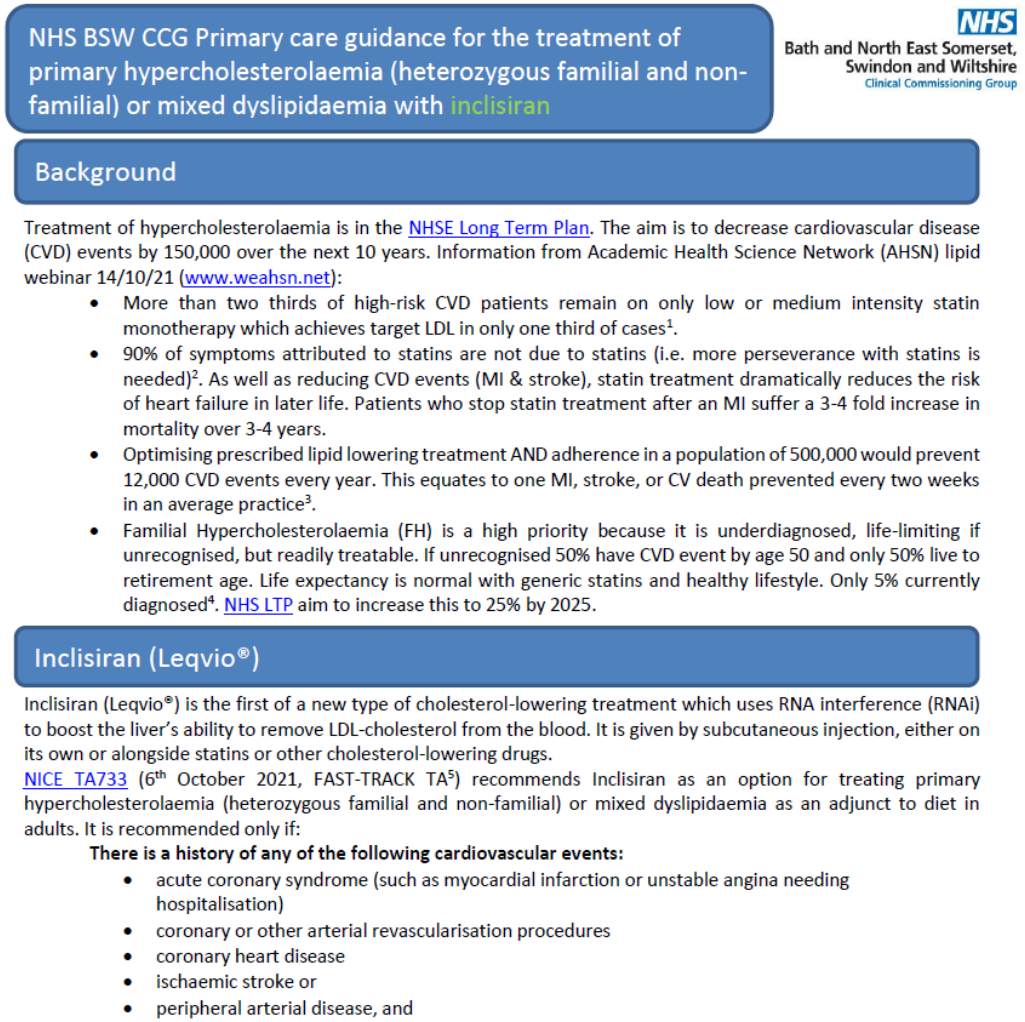
ORION-1: effects on LDL-cholesterol
(two-dose start)



Adverse-effects

- From ORION-1 but no side-effects listed in the BNF.
- The most common adverse events (occurring in >2% of patients) were myalgia, headache, fatigue, nasopharyngitis, back pain, hypertension, diarrhoea and dizziness.
- The incidences of these adverse events were not significantly different between groups receiving inclisiran and those receiving placebo.

Information about Inclisiran



NHS BSW CCG Primary care guidance for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia with inclisiran

NHS
Bath and North East Somerset, Swindon and Wiltshire
Clinical Commissioning Group

Background

Treatment of hypercholesterolaemia is in the NHSE Long Term Plan. The aim is to decrease cardiovascular disease (CVD) events by 150,000 over the next 10 years. Information from Academic Health Science Network (AHSN) lipid webinar 14/10/21 (www.weahsn.net):

- More than two thirds of high-risk CVD patients remain on only low or medium intensity statin monotherapy which achieves target LDL in only one third of cases[1].
- 90% of symptoms attributed to statins are not due to statins (i.e. more perseverance with statins is needed)[2]. As well as reducing CVD events (MI & stroke), statin treatment dramatically reduces the risk of heart failure in later life. Patients who stop statin treatment after an MI suffer a 3-4 fold increase in mortality over 3-4 years.
- Optimising prescribed lipid lowering treatment AND adherence in a population of 500,000 would prevent 12,000 CVD events every year. This equates to one MI, stroke, or CV death prevented every two weeks in an average practice[3].
- Familial Hypercholesterolaemia (FH) is a high priority because it is underdiagnosed, life-limiting if unrecognised, but readily treatable. If unrecognised 50% have CVD event by age 50 and only 50% live to retirement age. Life expectancy is normal with generic statins and healthy lifestyle. Only 5% currently diagnosed[4]. NHS LTP aim to increase this to 25% by 2025.

Inclisiran (Leqvio®)

Inclisiran (Leqvio®) is the first of a new type of cholesterol-lowering treatment which uses RNA interference (RNAi) to boost the liver's ability to remove LDL-cholesterol from the blood. It is given by subcutaneous injection, either on its own or alongside statins or other cholesterol-lowering drugs.

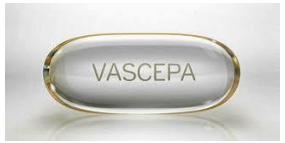
NICE TA733 (6th October 2021, FAST-TRACK TA[5]) recommends Inclisiran as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:

There is a history of any of the following cardiovascular events:

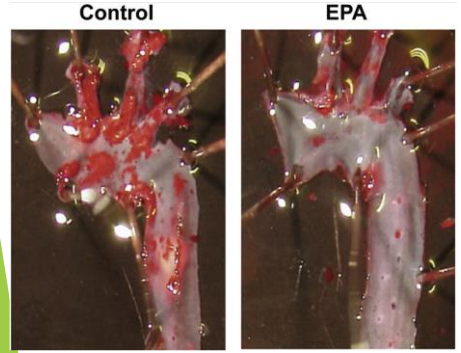
- acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
- coronary or other arterial revascularisation procedures
- coronary heart disease
- ischaemic stroke or
- peripheral arterial disease, and

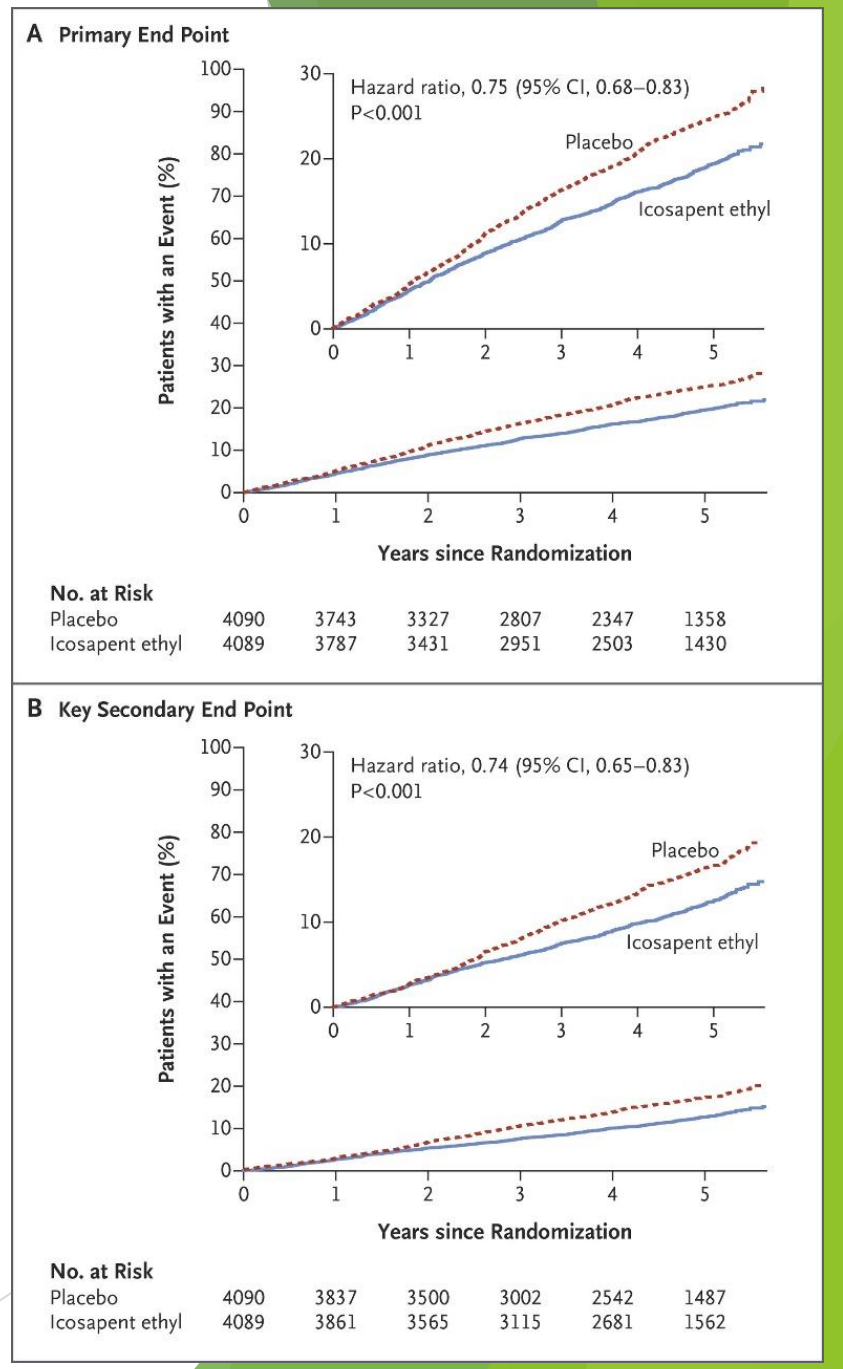
- http://bswformulary.nhs.uk/chaptersSubDetails.asp?FormularyID=5759&FormularySectionID=2&SubSectionRef=02.12&SubSectionID=A100#5759

Icosapent Ethyl (Vazkepa)



- Indication:
  - Adjunct to statin in prevention of cardiovascular events in hyperlipidaemia [in patients with triglycerides ≥ 1.7 mmol/L and either established cardiovascular disease, or diabetes with at least 1 other cardiovascular risk factor]
- MOA:
  - Likely multi-factorial: reduction of triglyceride-rich lipoproteins, anti-inflammatory and antioxidant effects, reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness/stability and antiplatelet effects → <u>stabilisation of atherosclerotic plaque</u>
- Cautions:
  - Antithrombotic treatment (bleeding time increased); history of atrial fibrillation or flutter
- Side-effects:
  - Arrhythmias; burping; constipation; gout; haemorrhage; pain; peripheral oedema; skin reactions





When to Refer to the Lipid Clinic

SPECIALIST LIPID MANAGEMENT CLINIC REFERRAL FORM	
Please tick reason for referral:	
Suspected Familial Hypercholesterolemia (FH) [see FH pathway, complete pre-referral assessment below and code referral with **Y35cf**]	
FH without cardiovascular disease (CVD) but LDL persistently above 5 mmol/l	
FH with CVD and LDL persistently above 3.5 mmol/l	
Severe hypercholesterolemia (TC >9 or non-HDL-C >7.5 mmol/l)	
Severe hypertriglyceridemia (1x triglycerides >20 mmol/l*, 2x >10 mmol/l) *TG>20 mmol/L At risk of acute pancreatitis. URGENT discussion with Secondary Care.	
Strong family history of premature CVD and mixed dyslipidaemia (raised TC and TG)	
Intolerance to medications; please first review statin intolerance pathway	
Other (please add reasons for referral in Clinical Details below)	
Family members of those with genetically confirmed FH will be contacted by the Lipid Service. No referral required.	

Suspected Familial Hypercholesterolaemia pre-referral assessment (see flow chart below)		
1	Confirmation that secondary causes optimised/excluded	YES NO
2	Result of **Simon Broome criteria** [code:XaR6H] **or** **Dutch lipid criteria** [code:XaaF1]	Simon Broome:<diagnoses> Dutch lipid score: <numerics>
3	Relevant personal or family CVD history (<60yrs) or family history of raised lipids.	

Clinical Reporting>Ardens Ltd>Contracts| 2022 23 | NCD Work to do> IIF CVD-04|?Refer to lipid service as age ≤ 29 years + Tot chol >7.5 or > 30 years + Tot chol >9

How to Assess for Familial Hypercholesterolaemia (FH)

For additional information see https://cks.nice.org.uk/topics/hypercholesterolaemia-familial/diagnosis/assessment-diagnosis/

and https://www.nice.org.uk/guidance/cg71

Search of patient records identifies previous FH genetic test but **uncoded diagnosis**?

Yes

Diagnosis read code • Heterozygous FH (inherited from 1 parent): X40X2 • Homozygous FH (inherited from 2 parents):

Treatment targets met?

Follow National Lipid Pathway. Aim for at least a 50% reduction of LDL (or non-HDL). Consider specialist referral IF they are at very high risk of a coronary event, 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.

Yes

Review lipid profile and CVD risk factors annually.

No

REFER TO SPECIALIST LIPID MANAGEMENT CLINIC.

No

Potential secondary cause identified?

Do secondary causes correlate with elevated cholesterol. Review historic results and update/add as necessary [full lipid profile, HbA1C and TSH, urine dip for protein, BMI, medications and alcohol intake].

Yes

Optimise secondary causes of hypercholesterolaemia

Review with repeat lipid profile in at least 3 months.

Lipid profile currently satisfactory

No

Yes

No

Family History?

Face to Face assessment using Simon Broome or Dutch Criteria [available via hyperlipidaemia template on SystmOne]. Obtain clear family history of **premature** CVD.

No

Follow National Lipid Pathway and optimise Lipid therapy.

Consider discussion with lipid clinic if still suspicious of FH

Yes

REFER TO SPECIALIST LIPID MANAGEMENT CLINIC.

Family History?

Face to Face assessment using Simon Broome or Dutch Criteria [available via hyperlipidaemia template on SystmOne]. Obtain clear family history of **premature** CVD.

No

Follow National Lipid Pathway and optimise Lipid therapy.

Yes

DISCUSS WITH SPECIALIST LIPID MANAGEMENT CLINIC.

Summary

- The lower the LDL-cholesterol the lower the risk of CVD
- For every 1 mmol/L LDL lowering there is 22% risk reduction in MI after a year's treatment
- New PCSK9 Inhibitor drugs have changed lipid management and allowed the lowest recommended targets to be achieved.
- The Joint British Societies recommend a non-HDL cholesterol target <2.5 mmol/L in secondary prevention patients.

Questions?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