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Find Assess Correct Treat Sustain
Cardiovascular Disease

Lipid Optimisation

Handbook

The purpose of this document is to provide a reference for primary care to help support the implementation of lipid optimisation.

Academic Health Science Network
North East and North Cumbria

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Why we need to find patients at risk of CVD

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

Screen

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

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

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

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

CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein-cholesterol; LLT, lipid-lowering therapy.

1. Kotseva, et al. *Eur J Prev Cardiol.* 2016;23:636–648; 2. Vallejo-Vaz and Ray. *Atherosclerosis.* 2018;277:289–297; 3. Nordestgaard, et al. *Eur Heart J.* 2013;34:3478–3490; 4. Mach, et al. Eur Heart J. 2019 Aug 31. pii: ehz455. doi: 10.1093/eurheartj/ehz455. [Epub ahead of print]; 5. Baigent, et al. *Lancet.* 2005:366;1267–1278; 6. CTT Collaboration. *Lancet.* 2010;376:1670–81; 7. Cannon, et al. *N Engl J Med.* 2015;372:2387–2397; 8. Sabatine, et al. *N Engl J Med.* 2017;376:1713–1722; 9. Schwartz, et al. *N Engl J Med.* 2018;379:2097–2107.

RECOMMENDED TREATMENT GOALS FOR LDL-C LOWERING THERAPY: 2016 VS 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8–3.5 mmol/L (70–135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100 mg/dL) or >50% ↓ if LDL-C 2.6–5.2 mmol/L (100–200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50%↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	<2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

For patients with ASCVD experiencing a second vascular event within 2 years while taking maximumly tolerated statin and ezetimibe therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) is recommended

LDL-C = low-density lipoprotein cholesterol.
Adapted from: Catapano AL, et al. Eur Heart J 2016;37:2999-3058. Mach F, et al. Eur Heart J 2019. doi:10.1093/eurheartj/ehz455. Epub ahead of print.

Identifying Patients at High-Risk and Very-High-Risk of CVD in Your Clinical Practice

ID

Look out for any patients:

- With a prior CVD event
- With family history of CVD or raised LDL-C
- With diabetes
- With other risk factors for CVD
  - Poor lipid profile
  - Hypertension
  - Obesity
  - Smoking
  - Physical inactivity
  - High CRP
  - Age, race, male sex

CRP, C-reactive protein; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol.

1. Mach, et al. *Eur Heart J*. 2019 Aug 31. pii: ehz455. doi: 10.1093/eurheartj/ehz455. [Epub ahead of print]; 2. NCEP. *Circulation*. 2002;106:3143–3421; 3. Jellinger, et al. *Endocr Pract*. 2012;18(suppl 1):1–78; 4. Cozlea, et al. *Curr Health Sci J*. 2013;39:225–231.

Primary Care Plays a Critical Role in the Management of Patients with High-risk and Very-high-risk CVD

Screen

- Screening for patients with established risk factors for CVD
- Online tools can help with patient screening

ID

- Look out for high-risk and very-high-risk CVD patients to ensure optimal treatment
- Use available tools, scoring criteria and guidelines as appropriate

Optimise

- Investigate possible reasons for sub-optimal lipid lowering
- Explore options to improve cholesterol levels, including adherence

Refer

- Refer patients to specialist care when attempts to attain target cholesterol levels are not successful

Lipid Optimisation

Routine monitoring in all patients (primary and secondary prevention)

• Measure total cholesterol, HDL-C and non-HDL cholesterol at 3 months after initiation or dose titration, ALT after 3 months and 12 months but not again unless clinically indicated as per NICE CG181. If LFTs are abnormal and statin treatment is stopped, the patient can be rechallenged if ALT < 3 x normal on retesting.

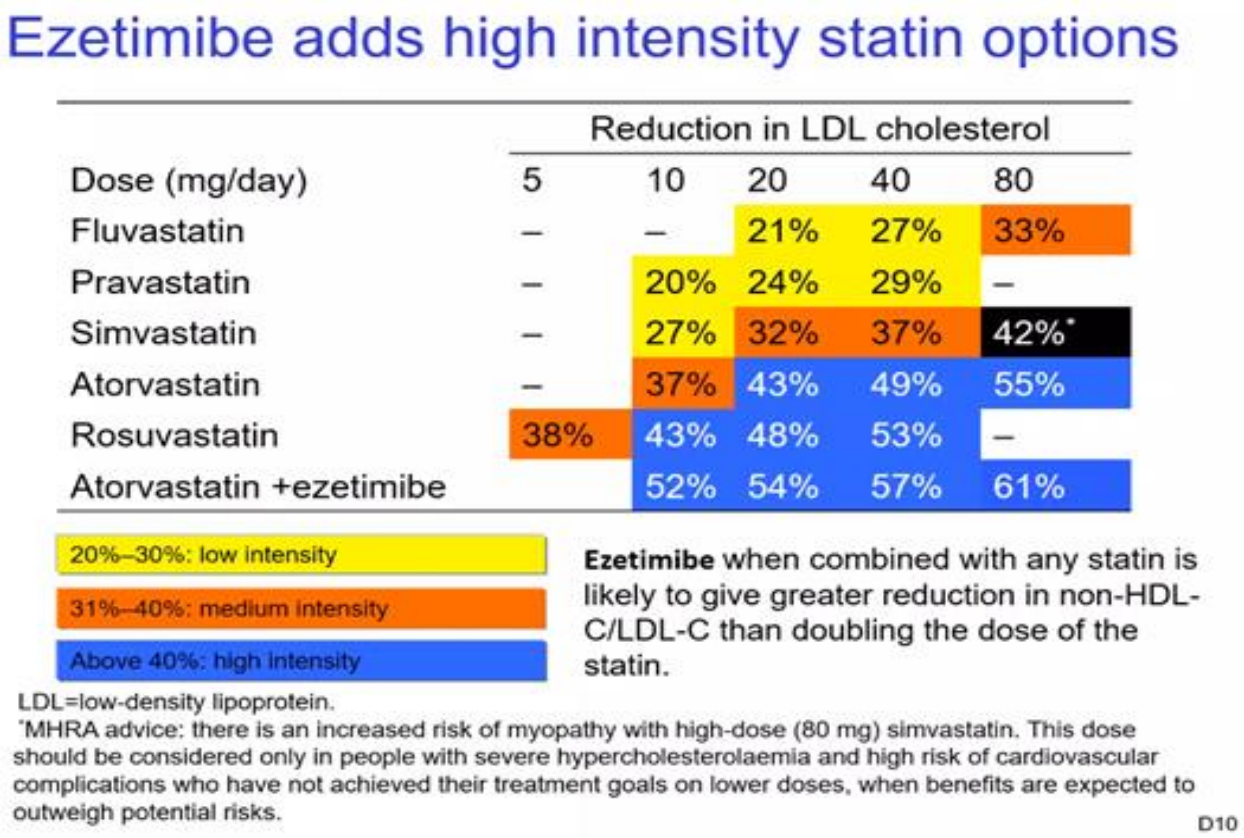
• If non-HDL cholesterol reduction < 40%, discuss treatment concordance, lifestyle measures, consider increasing dose of atorvastatin if not maximal.

• Ensure annual review

• Start atorvastatin 80 mg od.

• After 3 months if non-HDL c reduction of 40% and/or target of 2.5mmol/L is not achieved, add ezetimibe 10 mg od.

The table describes average percent reduction in LDL cholesterol with different statins/doses (taken daily). Similar reductions in non-HDL cholesterol can be assumed.



** Rosuvastatin 40mg is contraindicated in patients on Clopidogrel.

• If recommended statin treatment is contraindicated or not tolerated –

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)

Severe Hyperlipidaemia / Familial Hypercholesterolaemia (FH)

Consider the possibility of familial hypercholesterolaemia and investigate as described in familial hypercholesterolaemia (NICE guideline CG71) if they have:

- a total cholesterol concentration more than 7.5 mmol/litre **and**
- a family history of premature coronary heart disease.

1. Arrange for specialist assessment of people with a total cholesterol concentration of more than 9.0 mmol/litre or a non-HDL cholesterol concentration of more than 7.5 mmol/litre even in the absence of a first-degree family history of premature coronary heart disease.

2. Refer for urgent specialist review if a person has a triglyceride concentration of more than 20 mmol/litre that is not a result of excess alcohol or poor glycaemic control.

3. In people with a triglyceride concentration between 10 and 20 mmol/litre:
   - Repeat the triglyceride measurement with a fasting test (after an interval of 5 days, but within 2 weeks) **and**
   - Review for potential secondary causes of hyperlipidaemia **and**
   - Seek specialist advice if the triglyceride concentration remains above 10 mmol/litre.

4. In people with a triglyceride concentration between 4.5 and 9.9 mmol/litre:
   - Be aware that the CVD risk may be underestimated by risk assessment tools **and**
   - Optimise the management of other CVD risk factors present **and**
   - Seek specialist advice if non-HDL cholesterol concentration is more than 7.5 mmol/litre.

5. If a person has acute coronary syndrome, **DO NOT DELAY statin treatment**. Take a lipid sample on admission and about 3 months after the start of treatment.
6. Start statin treatment in people with CVD with atorvastatin 80 mg[6]. Use a lower dose of atorvastatin if any of the following apply:

   - potential drug interactions
   - high risk of adverse effects
   - patient preference.

   For information about implementing this recommendation, see implementation: getting started.

7. **DO NOT DELAY statin treatment** in secondary prevention to manage modifiable risk factors.

8. If a person has acute coronary syndrome, **DO NOT DELAY statin treatment**. Take a lipid sample on admission and about 3 months after the start of treatment.

9. Measure total cholesterol, HDL cholesterol and non-HDL cholesterol in all patients who have been started on high-intensity statin treatment (both primary and secondary prevention, including atorvastatin 20 mg for primary prevention) at 3 months of treatment and aim for a greater than 40% reduction in non-HDL cholesterol. If a greater than 40% reduction in non-HDL cholesterol is not achieved:

   - discuss adherence and timing of dose

- optimise adherence to diet and lifestyle measures

- consider increasing the dose if started on less than atorvastatin 80 mg and the person is judged to be at higher risk because of comorbidities, risk score or using clinical judgement.

10. Provide annual medication reviews for people taking statins.
    - Use these reviews to discuss medicines adherence and lifestyle modification and address CVD risk factors.
    - Consider an annual non-fasting blood test for non-HDL cholesterol to inform the discussion.
11. Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.
    For information about implementing this recommendation, see implementation: getting started.

The following doses for statins are high intensity, based on the percentage reduction in low density lipoprotein (LDL) cholesterol they can produce:

- atorvastatin: 20–80 mg
- rosuvastatin: 10–40 mg

What is Familial Hypercholesterolaemia (FH)?

Autosomal dominant genetic condition which 'doubles' bad cholesterol from the day of birth. Risk of CVD is much increased and premature heart attack <60 yrs is more common. We use the Simon Broome and/or Dutch Lipid Clinic Network Score (DLCNS) criteria to identify patients in whom this condition may be present.

Further scoring can take place with the information available to determine whether genetic testing may be successful in identifying a mutation in the DNA to cause the condition. If a mutation can be identified, further testing of offspring/relatives can then be offered. This is facilitated by the FH Service.

The NHS ten year plan, published 2019, aims to identify 25% of patients with this condition by 2024. We are at around <9% currently. There is a further drive to identify cases in primary care and anyone <30yrs with a total cholesterol >7.5mmol/L or 30+yrs with a cholesterol of 9mmol/L or above should be considered as to whether they may be at risk of the condition (often excluding other conditions which cause high cholesterol).

Familial Hypercholesterolaemia is Caused by Mutations of Proteins Involved in LDL-C Metabolism

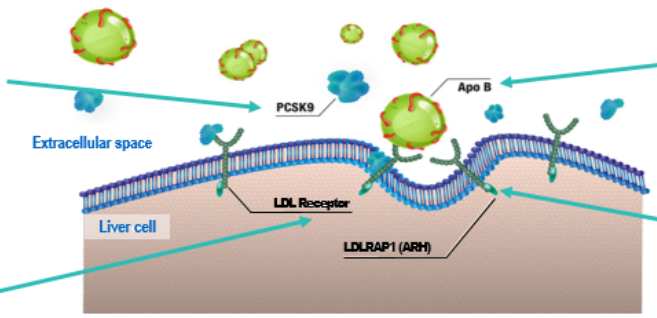
Familial hypercholesterolaemia is the lifelong elevation of LDL-C levels[1]

Mutations in key proteins involved in LDL metabolism lead to reduced uptake of LDL by hepatocytes and thus elevated serum LDL-C levels[1,2]

Key Proteins Involved in LDL Uptake

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

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



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

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

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

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

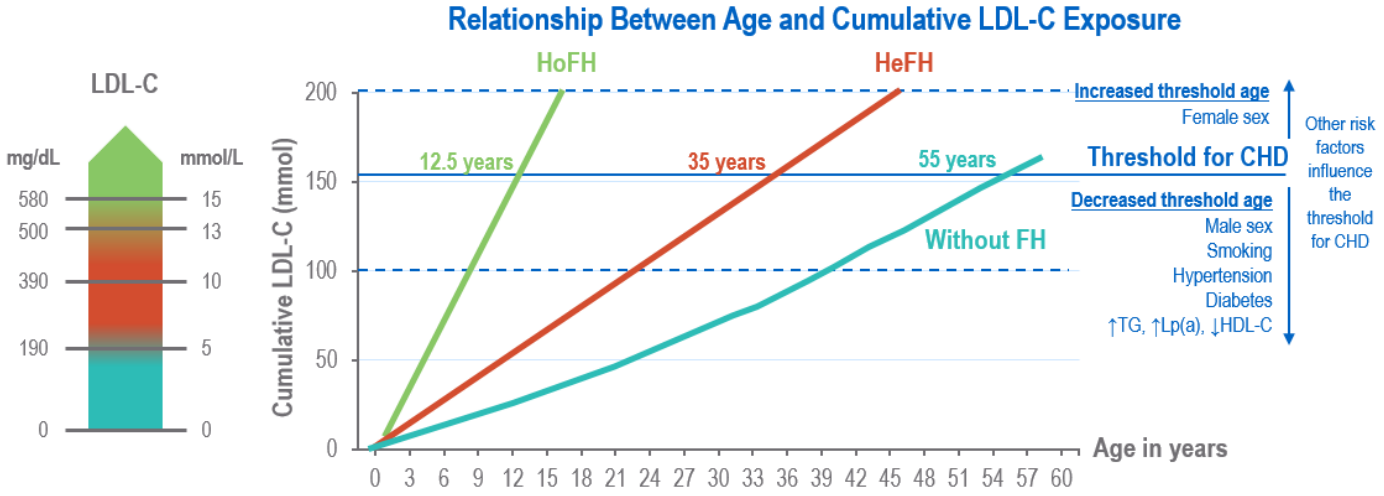
Characteristics of Homozygous and Heterozygous FH

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

*Subcutaneous cholesterol deposits in peripheral tissues;[9] †If left untreated, patients with HoFH die before the age of 20;[3,8] ‡For FH homozygotes, >40% of individuals will develop CHD before the age of 20.[10]
CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MI, myocardial infarction.

1. Bouhairie VE and Goldberg AC. *Cardiol Clin.* 2015;33:169–179; 2. Vallejo-Vaz and Ray. *Atherosclerosis.* 2018;277:289–297; 3. Nordestgaard, et al. *Eur Heart J.* 2013;34:3478-3490a; 4. NCEP. *Circulation.* 2002;106:3143–3421; 5. Raal and Santos. *Atherosclerosis.* 2012;223:262–268; 6. Reiner. *Nat Rev Cardiol.* 2015;12:565–575; 7. Robinson. *J Manag Care Pharm.* 2013;19:139–149; 8. Cuchel, et al. *Eur Heart J.* 2014;35:2146–2157; 9. Goldstein and Brown. *Arterioscler Thromb Vasc Biol.* 2009;29:431–438; 10. Soutar and Naoumova. *Nat Clin Pract Cardiovasc Med.* 2007;4:214–225.

FH Patients Reach LDL-C Threshold Levels for Chronic Heart Disease at an Early Age

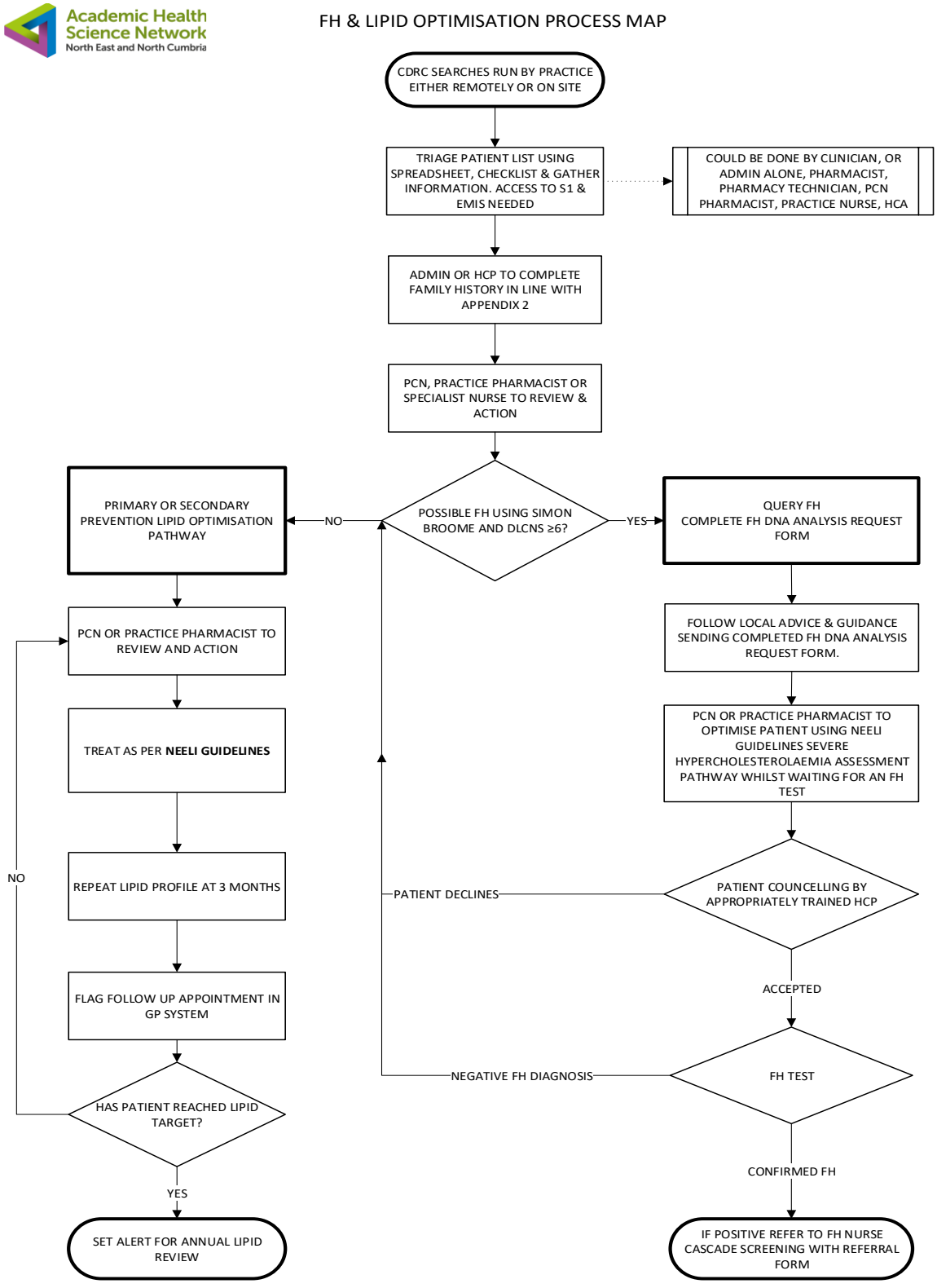


The horizontal blue line represents the theoretical threshold of the cumulative LDL-C exposure required for the development of CHD. This line may be higher or lower depending on the presence of other risk factors.

CHD, coronary heart disease; FH, familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); TG, triglyceride.

1. Cuchel, et al. *Eur Heart J.* 2014;35:2146–2157; 2. Nordestgaard, et al. *Eur Heart J.* 2013;34:3478–3490a.

HOW TO IDENTIFY PATIENTS FOR LIPID OPTIMISATION (INCLUDING FH)



Please see below a link to the Standard Operating Procedure document for '**Primary Care Lipid Lowering and Familial Hypercholesterolaemia (FH)'**. This is a guide to support Primary Care in identifying patients requiring lipid optimisation and those who may have FH.

LIPID MODIFICATION GUIDELINES

https://www.england.nhs.uk/aac/what-we-do/what-innovations-do-we-support/rapid-uptake-products/lipid-management/
https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/

NICE CG181 Guideline

https://www.nice.org.uk/guidance/cg181

NEELI Guidelines –

Guidelines include the flowchart and algorithms from the AAC guidelines

https://www.heartuk.org.uk/downloads/health-professionals/neeli-final-102.pdf
Please always refer to the most up to date version

Ezetimibe NICE TA 385

https://www.nice.org.uk/guidance/ta385

Bempedoic Acid NICE TA 694

https://www.nice.org.uk/guidance/ta694

Inclisiran NICE TA 733

https://www.nice.org.uk/guidance/ta733/documents/html-content-2

PCSK9i NICE TA393 (Alirocumab, Sanofi) and NICE TA 394 (Evolocumab, Amgen)

https://www.nice.org.uk/guidance/ta393

https://www.nice.org.uk/guidance/ta394

These were published in 2016 and provided a framework with respect to the prescribing of PCSK9i medications. See PCSK9i section for further detail.

Regional Lipid Structure

North of England (NEELI) lipid clinics are listed on page X of the NEELI Guidelines.

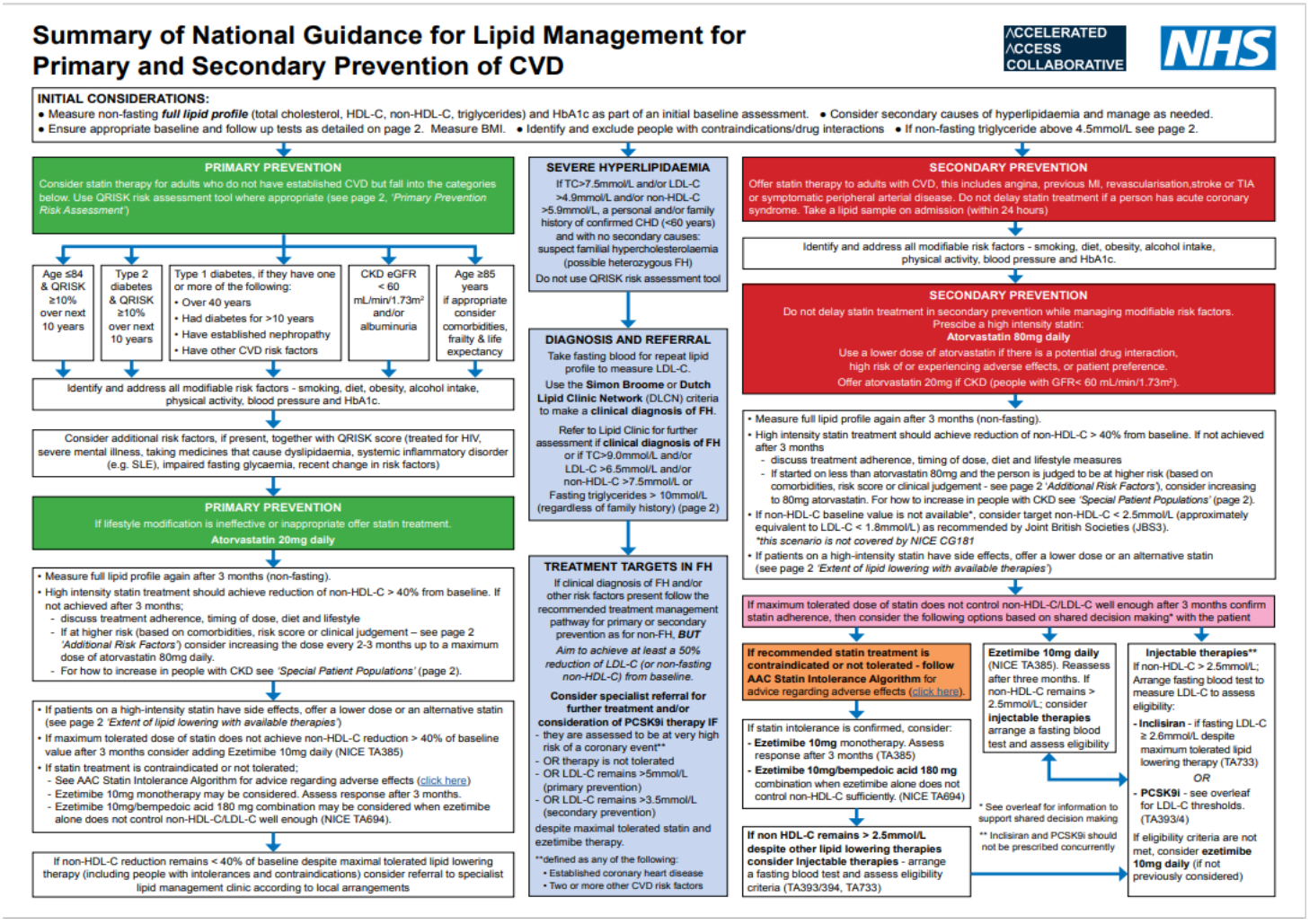
Lipid clinics are available around the country.

https://www.heartuk.org.uk/lipid-clinics/find-your-nearest-lipid-clinic

Lipid clinic clinicians are part of the Lipid Specialist Advisory Group (LSAG) which meets four times per year to discuss diagnosis, treatment, management and operational issues.

National Guidance for Lipid Management for Primary and Secondary Prevention (AAC Pathway)

Please always refer to the most up to date version:
https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/



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 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*/2.2)
*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.

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

ACCELERATED ACCESS COLLABORATIVE

NHS

Authors: Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. Nov 2021. Review date: Nov 2022. NICE endorsed Dec 2021.

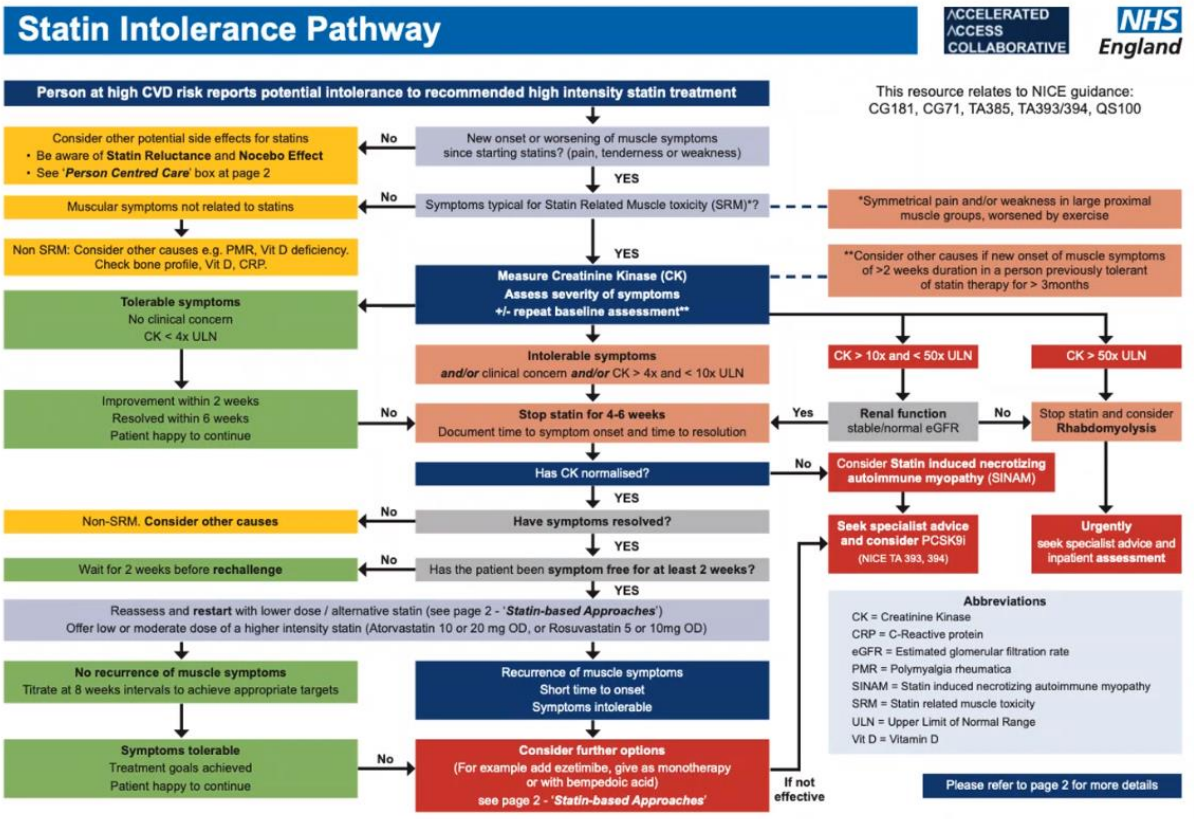
Approved by the National Institute for Health and Care Excellence (NICE), Dec 2021.

Statin intolerance pathway

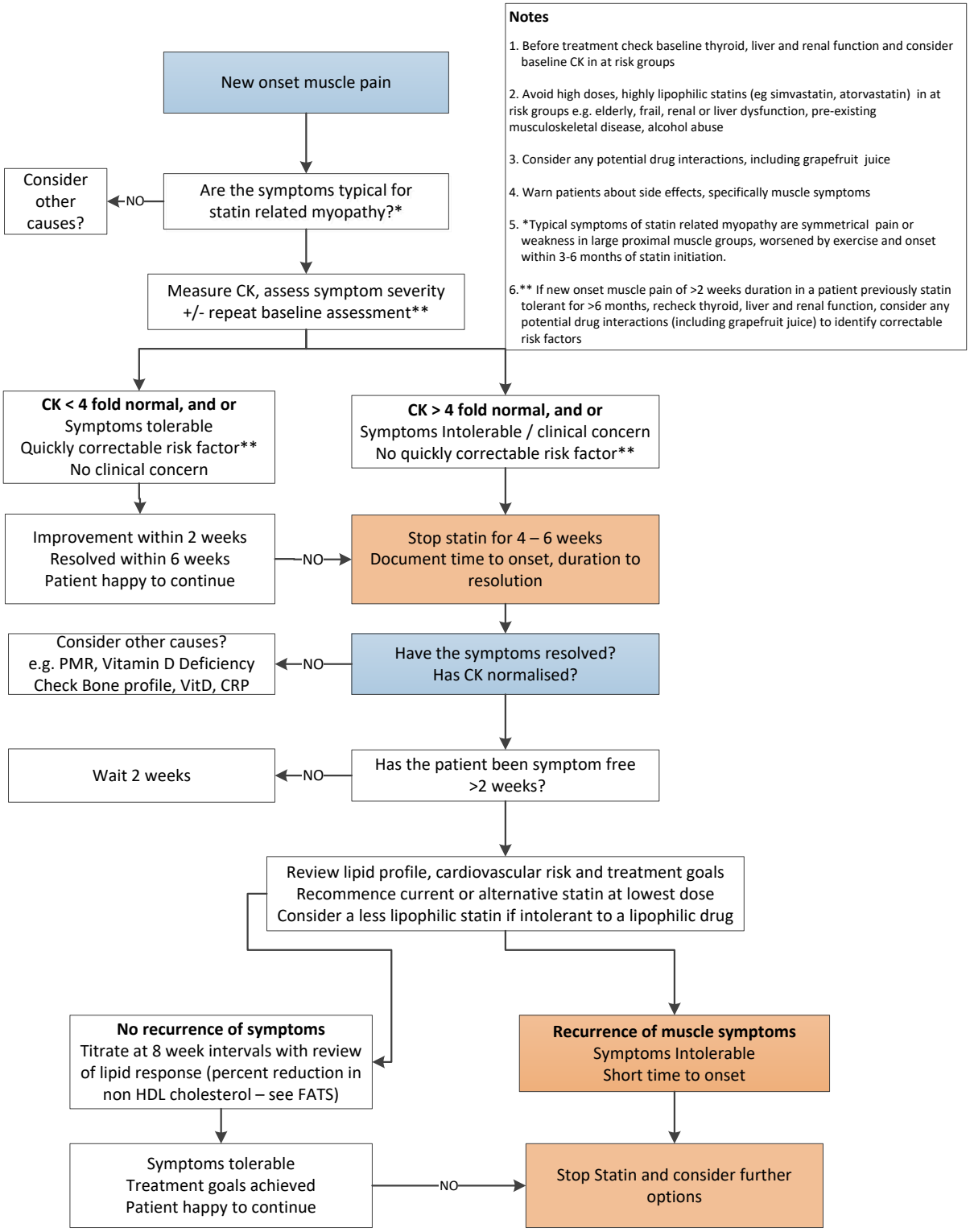
https://www.england.nhs.uk/aac/publication/statin-intolerance-pathway/

https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-Intolerance-Pathway-NEW.pdf

For patients who complain of muscle related symptoms following the initiation of a statin the following flow chart which is taken from NEELI should be used. Clinical teams should be directed to its use and advised to refer for consideration of Ezetimibe, Bempedoic Acid, Inclisiran or PCSK9i if patient is unable to tolerate High Intensity Statins.



Flowchart for Assessment of Suspected Statin Related Myopathy



The Simon Broome Criteria and Dutch Lipid Clinics Network Criteria

The Simon Broome Criteria

A: Definite familial hypercholesterolaemia is defined as:

Total cholesterol greater than 6.7mmol/L or low density lipoprotein cholesterol (LDL-C) greater than 4.0mmol/L in a child aged younger than 16 years or total cholesterol greater than 7.5mmol/L or LDL-C greater than 4.9mmol/L in an adult (levels either pre-treatment or highest on treatment).

Plus:

Tendon xanthomas in patient or in 1st degree relative (parent, sibling, child) or in 2nd degree relative (grandparent, uncle, aunt)

Or:

DNA-based evidence of an LDL receptor mutation or familial defective apo B-100 or a PCSK9 mutation

B: Possible Familial Hypercholesterolaemia is defined as:

Total cholesterol greater than 6.7mmol/L or low density lipoprotein cholesterol (LDL-C) greater than 4.0mmol/L in a child aged younger than 16 years or total cholesterol greater than 7.5mmol/L or LDL-C greater than 4.9mmol/L in an adult (levels either pre-treatment or highest on treatment)

and at least one of the following:

Family history of myocardial infarction: younger than 50 years of age in a 2nd degree relative or younger than 60 in a 1st degree relative

Or:

Family history of raised cholesterol greater than 7.5mmol/L in adult 1st or 2nd degree relative or greater than 6.7mmol/L in child or sibling aged younger than 16 years

https://www.heartuk.org.uk/cholesterol/fh-diagnosis-criteria
https://www.nice.org.uk/guidance/cg71/evidence/full-guideline-appendix-f-pdf-241917811

The Dutch Lipid Clinics Network Criteria

The Dutch Lipid Clinical Network criteria is used in the Netherlands to diagnose FH, but it's sometimes used by doctors in Britain too. It works on a points system, where a set number of points are given to certain signs and symptoms, your cholesterol levels and illnesses in your family.

- a total point score of greater than 8 is considered "definite FH"
- a total point score of 6-8 is considered "probable FH"
- a total point score of 3-5 is considered "possible FH"

https://www.mdcalc.com/dutch-criteria-familial-hypercholesterolemia-fh

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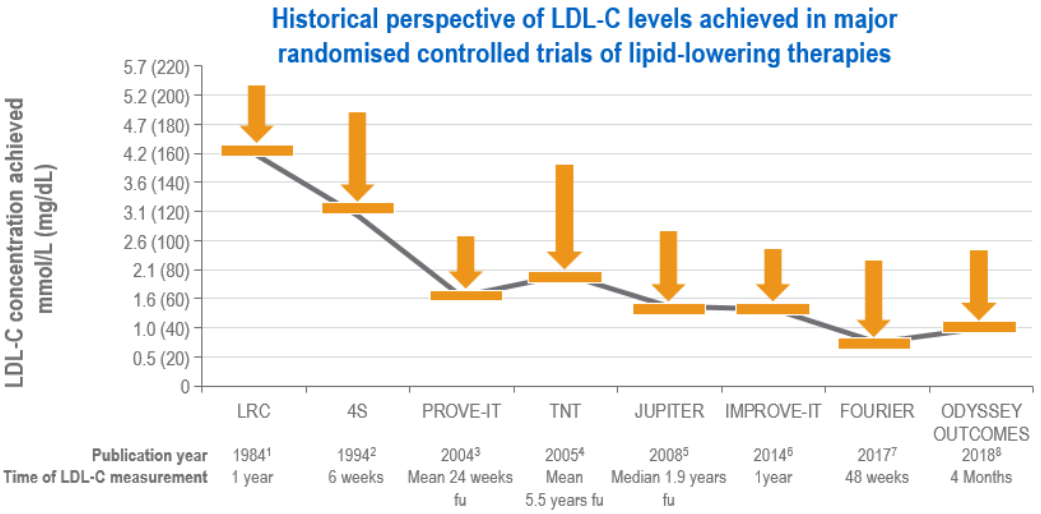
EVIDENCE FOR LIPID OPTIMISATION

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



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

Figure adapted from: Masana, et al. *J Clin Lipidol.* 2018;12(2):292-299.e3. Orange arrows indicate the mean LDL decrease obtained in the study.
fu, follow up; LDL-C, low-density lipoprotein-cholesterol.
1. Lipid Research Clinics. *JAMA.* 1984;251:351–364; 2. Scandinavian Simvastatin Survival Study (4S) Group. *Lancet.* 1994;344:1383–1389; 3. Cannon, et al. *N Engl J Med.* 2004;350:1495–1504; 4. LaRosa, et al. *N Engl J Med.* 2005;352:1425–1435; 5. Ridker, et al. *N Engl J Med.* 2008;359:2195–220; 6. Cannon, et al. *N Engl J Med.* 2015;372:2387–2397; 7. Sabatine, et al. *N Engl J Med.* 2017;376:1713–1722; 8. Schwartz, et al. *N Engl J Med.* 2018;379:2097–2107.

- LRC: Lipid Research Clinics trial
- 4S: Scandinavian Simvastatin Survival Study
- PROVE -IT: Pravastatin or Atorvastatin
- TNT: Treating to new Targets. Atorvastatin
- JUPITER: Rosuvastatin
- IMPROVE -IT: Ezetimibe
- FOURIER: Evolocumab (PCSK9i)
- ODYSSEY: Alirocumab (PCSK9i)

Bempedoic Acid - Trials

https://www.medicines.org.uk/emc/product/11743/smpc

The efficacy of bempedoic acid was investigated in four multi-centre, randomised, double-blind, placebo-controlled trials involving 3,623 adult patients with hypercholesterolaemia or mixed dyslipidaemia, with 2,425 patients randomised to bempedoic acid. All patients received bempedoic acid 180 mg or placebo orally once daily. In two trials, patients were taking background lipid-modifying therapies consisting of a maximum tolerated dose of statin, with or without other lipid-modifying therapies. Two trials were conducted in patients with documented statin intolerance. The primary efficacy endpoint in all Phase 3 trials was the mean percent reduction from baseline in LDL-C at week 12 as compared with placebo.

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IMPROVE-IT trial – Ezetimibe

https://www.medicines.org.uk/emc/product/9109/

Published in 2015, the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) randomized 18,144 patients with ACS to simvastatin 40 mg/d plus ezetimibe 10 mg/d or simvastatin alone. With median follow-up of 6 years, simvastatin + ezetimibe was found to reduce the primary outcome of CV mortality, major CV event, or nonfatal stroke (34.7% vs. 32.7%; P=0.016; NNT 50). There was no reduction in all-cause or CV mortality with simvastatin + ezetimibe, though there was a reduction in MI and stroke.

ORION trials (pooled analysis) – Inclisiran

https://www.medicines.org.uk/emc/product/12039/smpc

In the phase III pooled analysis, subcutaneously administered Inclisiran lowered LDL-C between 50% and 55% as early as day 90 (Figure 1), which was maintained during long-term therapy. Maximal LDL-C reduction was achieved at day 150 following a second administration. Small but statistically significant increased LDL-C reductions up to 65% were associated with lower baseline LDL-C levels (approximately <2 mmol/l [77 mg/dl]), higher baseline PCSK9 levels and higher statin doses and statin intensity.

The efficacy of inclisiran was evaluated in three phase III studies in patients with atherosclerotic cardiovascular disease (ASCVD) (coronary heart disease, cerebrovascular disease or peripheral artery disease), ASCVD risk equivalents (type 2 diabetes mellitus, familial hypercholesterolaemia, or 10-year risk of 20% or greater of having a cardiovascular event assessed by Framingham Risk Score or equivalent) and/or familial hypercholesterolaemia (FH). Patients were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional LDL-C reduction (patients unable to reach their treatment goals). Approximately 17% of patients were statin intolerant. Patients were administered subcutaneous injections of 284 mg inclisiran or placebo on day 1, day 90, day 270 and day 450. Patients were followed until day 540.

Fourier – Evolocumab (140mg fortnightly/420mg Monthly)

https://www.medicines.org.uk/emc/medicine/30628

Among patients with clinical atherosclerotic disease and a baseline LDL of 2.4mmol/L despite high- or moderate-intensity statin therapy (70% high intensity) and followed up for a median of 26 months, the addition of Evolocumab resulted in a reduction in LDLC at 48 weeks of 59% together with an absolute risk reduction of the hard MACE composite endpoint (key secondary endpoint) of 1.3 % at 2 years and 2 % at 3 years, driven primarily by reductions in nonfatal MI, stroke, and revascularization. There was no overall or CV-specific mortality benefit with Evolocumab. Other than a modest 2% incidence in injection-site reactions, there was no increase in key adverse events including new-onset diabetes or neurocognitive effects in patients receiving Evolocumab.

Odyssey – Alirocumab (75mg/150mg fortnightly)

https://www.medicines.org.uk/emc/product/8093/

https://www.medicines.org.uk/emc/product/7146/

In patients who had an acute coronary syndrome 1-12 months earlier, followed up for 2.8 years, the use of the monoclonal antibody alirocumab in addition to high-intensity statin therapy with a baseline LDL-C of 2.38mmol/L resulted in an additional on treatment reduction in LDL cholesterol at 48 weeks of 54% with no significant increase in serious adverse events. Furthermore, a *post-hoc* analysis demonstrated a 2% absolute risk reduction in major adverse cardiovascular events with alirocumab therapy in patients with a baseline LDL-C> 2.6mmol/L.

PCSK9i Eligibility

Patients must meet the NICE eligibility criteria, see table below. Locally statin intolerance can be defined after 2 or more (different classes) of statin have been trialled.

	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	

[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

Assessing suitability for PCSK9i medication

Patients who are intolerant of oral medications should have tried the medications documented below and sustained document side effects, or fail to achieve the targets as stated by NICE guidelines;

-Statins
-Bempedoic Acid / Ezetimibe

Patients should be asked the following questions;

- Are they willing to undergo self-administered fortnightly injections and commit to collection of drug initially then we would work towards home delivery
- Initially more intensive (2-3 monthly) blood testing will be required
- Do they have a known latex allergy (contraindication to the injectables)
- They can bring a friend/relative to be trained

Blood tests to be checked prior to prescription

-eGFR should be >30
-Assess for LFT abnormality- specifically low albumin/high bilirubin. Minor enzyme abnormalities are not a contraindication to treatment.

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Initiation/training

Homecare can be set up for both medications. This requires agreement from the patient and submission of a prescription, see appendix for forms.

Follow up and enquiries for repeat prescriptions

Patients are required to be on a three to six monthly follow up in the lipid clinic until further instructions depending on the local Trust. Prescriptions cannot be issued from primary care without a Primary Care Rebate Scheme. Requests for prescriptions should be passed to the appropriate clinician and on enquiry the patient details should be taken, and they should be asked if they have had their fasting blood tests taken. If not, they should be supplied a form for Fasting Lipids, ALT and creatinine with the clinical details 'on PCSK9 inhibitor'. All details of requests should be passed to the appropriate consultant or clinician.

Patients will be trained either in the Lipid Clinic or via Homecare on how to self-administer PCSK9i.

Follow up

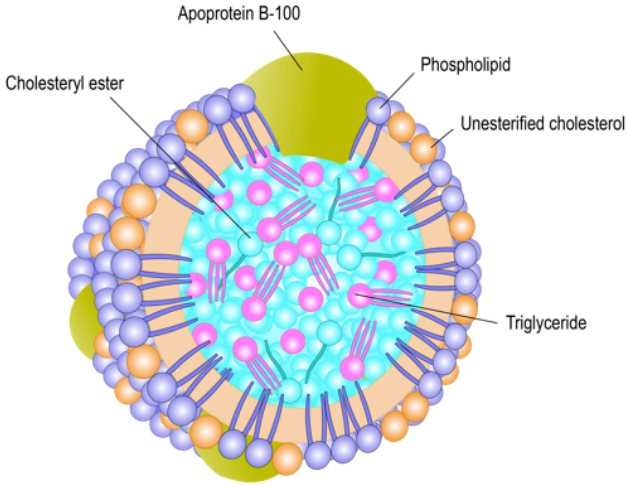
- If the patient has any further uncertainties on self-administering the drug they should contact the lipid clinic before the drug is injected.
- After 8-10 weeks a repeat lipid profile is required to assess response (ensure the patient has a blood test request form – Fasting lipid profile, ALT, Creatinine- with clinical details 'on PCSK9 inhibitor')
- Report any adverse effects to appropriate secondary care clinician
- Three-month prescription, all future prescriptions must be obtained from appropriate secondary care clinician. Please call after 8-10 week lipid tests have been taken
- Patient is given a form for fasting lipid profile at 8-10 weeks following appointment/initiation

LIPID EDUCATION

The Lipoprotein Complex

The Lipoprotein Complex

Components of an LDL Particle[1]



LIPOPROTEIN COMPLEXES[1,2]

- Packaging of cholesterol and triglycerides for transport through the blood[1,2]
  - At the core: triglycerides and cholesterol esters
  - Surrounding layer: phospholipids, free (unesterified) cholesterol and apolipoproteins

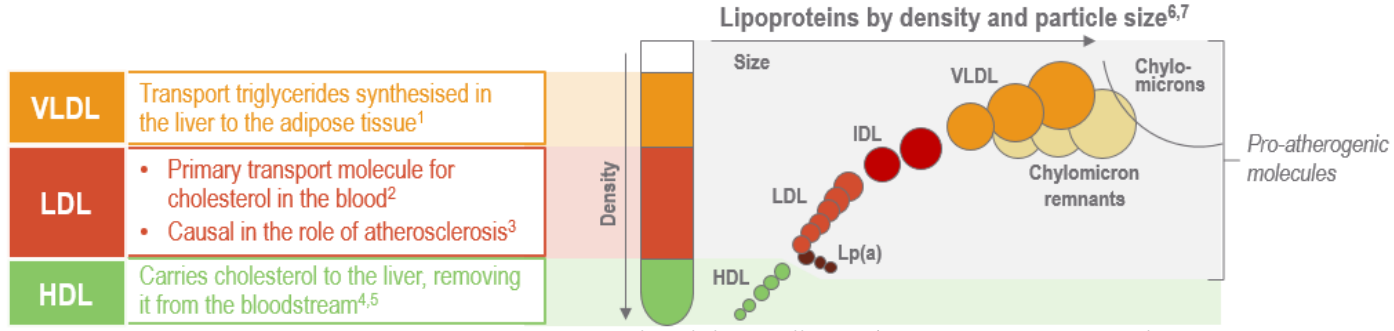
APOLIPOPROTEINS[3]

- Surface proteins with structural and metabolic functions, including as ligands for specific receptors
- There are many different apolipoproteins with varying functions
- The presence of a specific apolipoprotein can indicate the presence of a specific lipoprotein in the blood:
  - **ApoB100:** Found in VLDL, IDL and LDL
  - **ApoCI:** Found in chylomicrons, VLDL and HDL
  - **ApoE:** Found in chylomicron remnants, VLDL and HDL

HDL, high-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; VLDL, very low-density lipoprotein.
1. Semenkovich, et al. Disorders of Lipid Metabolism. In: *Williams Textbook of Endocrinology*. 12th ed. 2011:1633–1674; 2. Harrold. Antihyperlipoproteinemics and inhibitors of cholesterol biosynthesis. In: *Foye's Principles of Medicinal Chemistry*. 7th ed; 2013:815–840; 3. Feingold and Grunfeld. Introduction to Lipids and Lipoproteins. [Updated 2018 Feb 2]. In: Feingold, et al. editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK305896/. Accessed December 2019.

Differentiating Lipoproteins

Lipoproteins by density and particle size[6,7]



VLDL — Transport triglycerides synthesised in the liver to the adipose tissue[1]

LDL
- Primary transport molecule for cholesterol in the blood[2]
- Causal in the role of atherosclerosis[3]

HDL — Carries cholesterol to the liver, removing it from the bloodstream[4,5]

LIPOPROTEIN COMPONENTS[6]

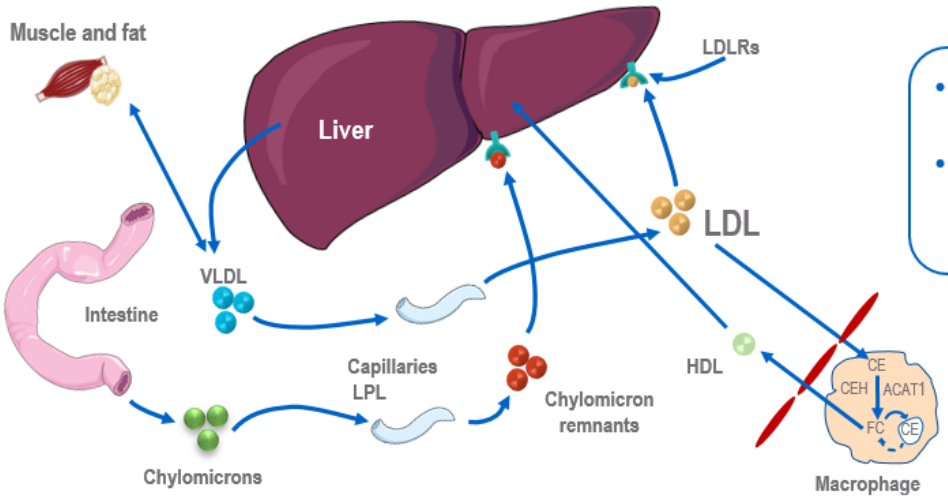
Triglycerides
- Store fatty acids, a major source of energy in the body
- All lipoproteins contain a core of triglycerides

Apolipoproteins
- Surface proteins with structural and metabolic function

HDL-C, high-density lipoprotein-cholesterol; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.
1. Hall and Guyton. Lipid Metabolism; In: *Guyton and Hall Textbook of Medical Physiology*. 13th ed; 2. Semenkovich, et al. Disorders of Lipid Metabolism. In: *Williams Textbook of Endocrinology*. 12th ed. 2011:1633–1674; 3. Ference, et al. *Eur Heart J*. 2017;38:2459–2472; 4. Harrold. Antihyperlipoproteinemics and inhibitors of cholesterol biosynthesis. In: Foye's Principles of Medicinal Chemistry. 7th ed; 2013:815–840; 5. Cox and Garcia-Palmieri. Cholesterol, triglycerides, and associated lipoproteins; In: *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. 1990:153–160; 6. Feingold and Grunfeld. Introduction to Lipids and Lipoproteins. [Updated 2018 Feb 2]. In: Feingold, et al. editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK305896/. Accessed December 2019; 7. Langlois, et al. *Clin Chem*. 2018;64:1006–1033.

Cholesterol

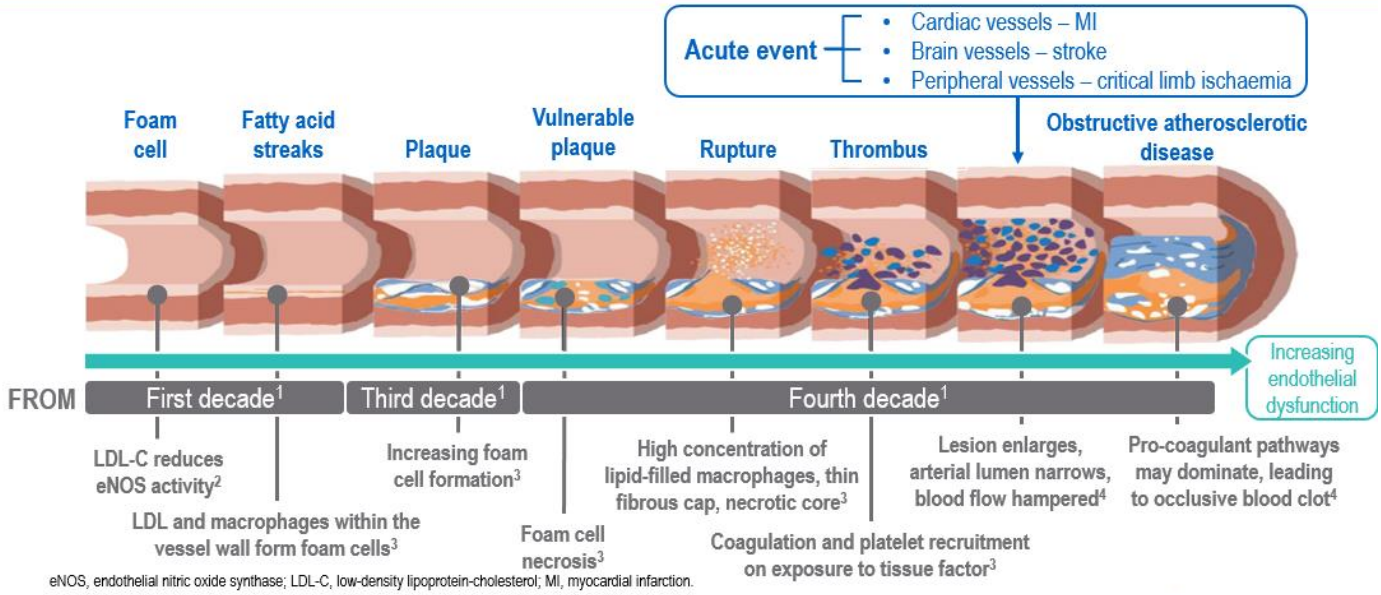
Cholesterol is Primarily Transported via LDL Particles in the Body



- 70% of plasma cholesterol is transported via LDL particles[1]
- LDL is formed from endogenous and exogenous pathways via VLDL[1,2]

ACAT1, acetyl coenzyme A acetyltransferase; CE, cholesterol ester; CEH, cholesterol ester hydrolase; FC, free cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.
1. Rader, et al. *J Clin Invest*. 2003;111:1795–1803. 2. Rudel, et al. *Arterioscler Thromb Vasc Biol*. 2005;25:1112–1118.

LDL-C and Atherosclerotic Plaque Formation



eNOS, endothelial nitric oxide synthase; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction.
1. Stary, et al. *Circulation*. 1995;92:1355–1374; 2. Davignon, et al. *Circulation*. 2004;109(23 Suppl 1):III27–II32; 3. Glass and Witztum. *Cell*. 2001;104:503–516; 4. Libby. *Nature*. 2002;420:868–874.

LIPID LOWERING THERAPIES

Lipid Lowering Therapies – How do they work?

Bempedoic Acid

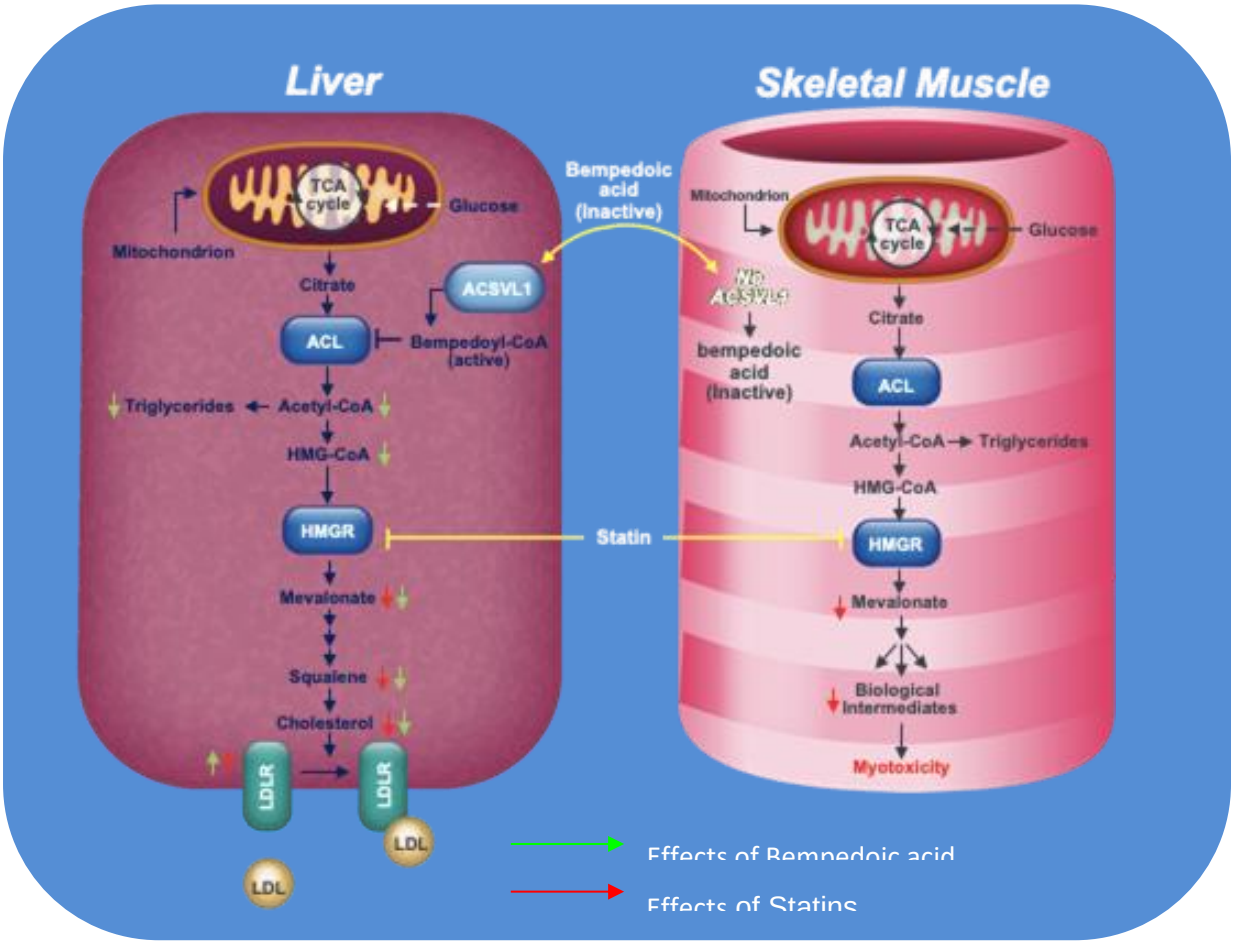
Mechanism of action

Bempedoic acid is a prodrug activated by ACSVL1, expressed primarily in the liver. ACSVL1, the activating enzyme of Bempedoic Acid, is expressed primarily in the liver and not in skeletal muscle.

Activated Bempedoic Acid inhibits the ATP-citrate lyase (ACL) enzyme in the liver. ACL is a key enzyme in the cholesterol biosynthesis pathway.

Resulting in decreased cholesterol synthesis in the liver

And lowers LDL-C levels in the blood via upregulation of LDL receptors



Adapted from Pinkosky SL, et al. 2016.

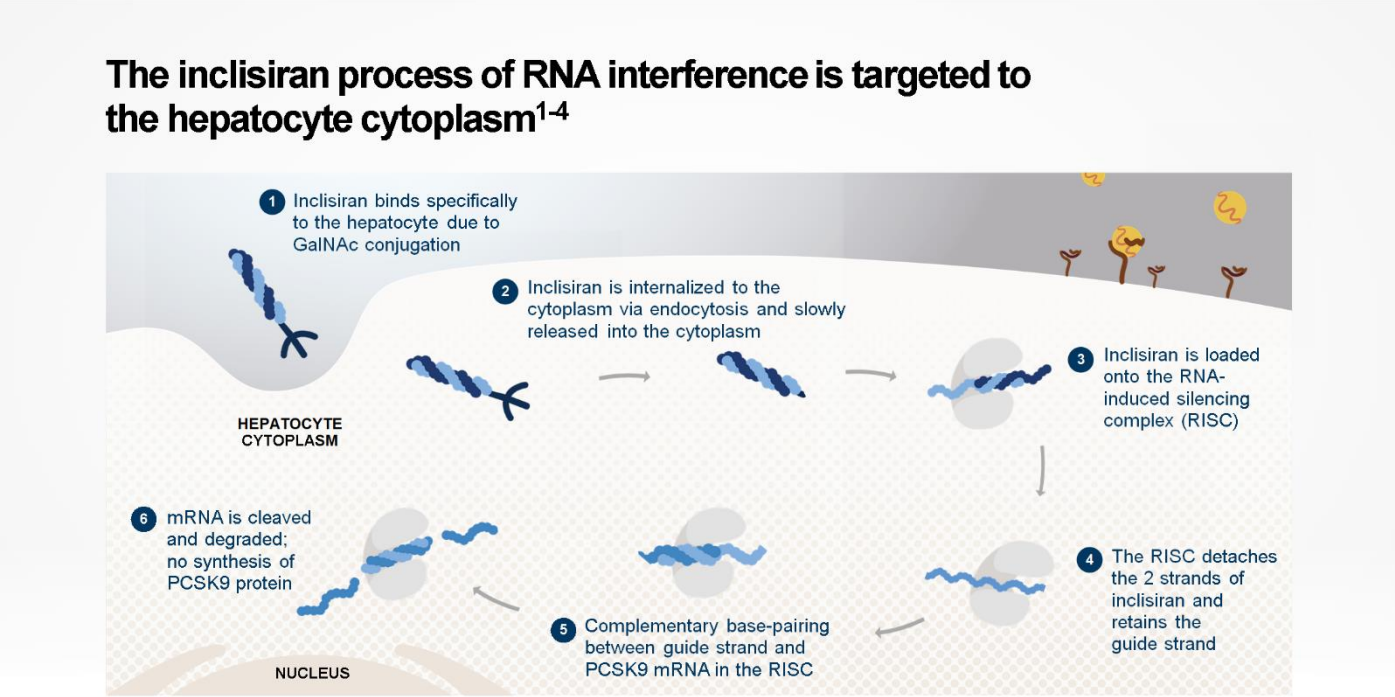
ACL: ATP-citrate lyase; ACSVL1: Very long-chain acyl-CoA synthetase-1; ATP: Adenosine triphosphate; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; HMGR: 3-hydroxy-3-methylglutarate-CoA reductase; LDL: Low-density lipoprotein cholesterol; LDLR: Low-density lipoprotein receptor; TCA: Tricarboxylic acid.

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 November 2021).

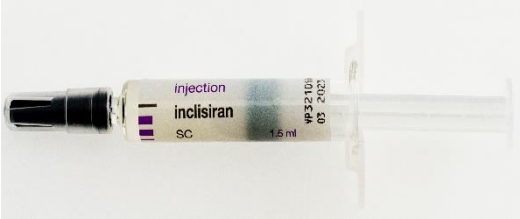
Inclisiran

Mechanism of action

Inclisiran is a cholesterol-lowering, double-stranded, small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilises the RNA interference mechanism and directs catalytic breakdown of mRNA for proprotein convertase subtilisin kexin type 9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.



1. Khvorova A, et al. *N Engl J Med*. 2017;376:4-7. 2. Fitzgerald K, et al. *N Engl J Med*. 2017;376:41-51.
3. Springer AD, et al. *Nucleic Acid Ther*. 2018;28:109-118. 4. Tsouka AN, et al. *Curr Pharm Des*. 2018;24:3622-3633.



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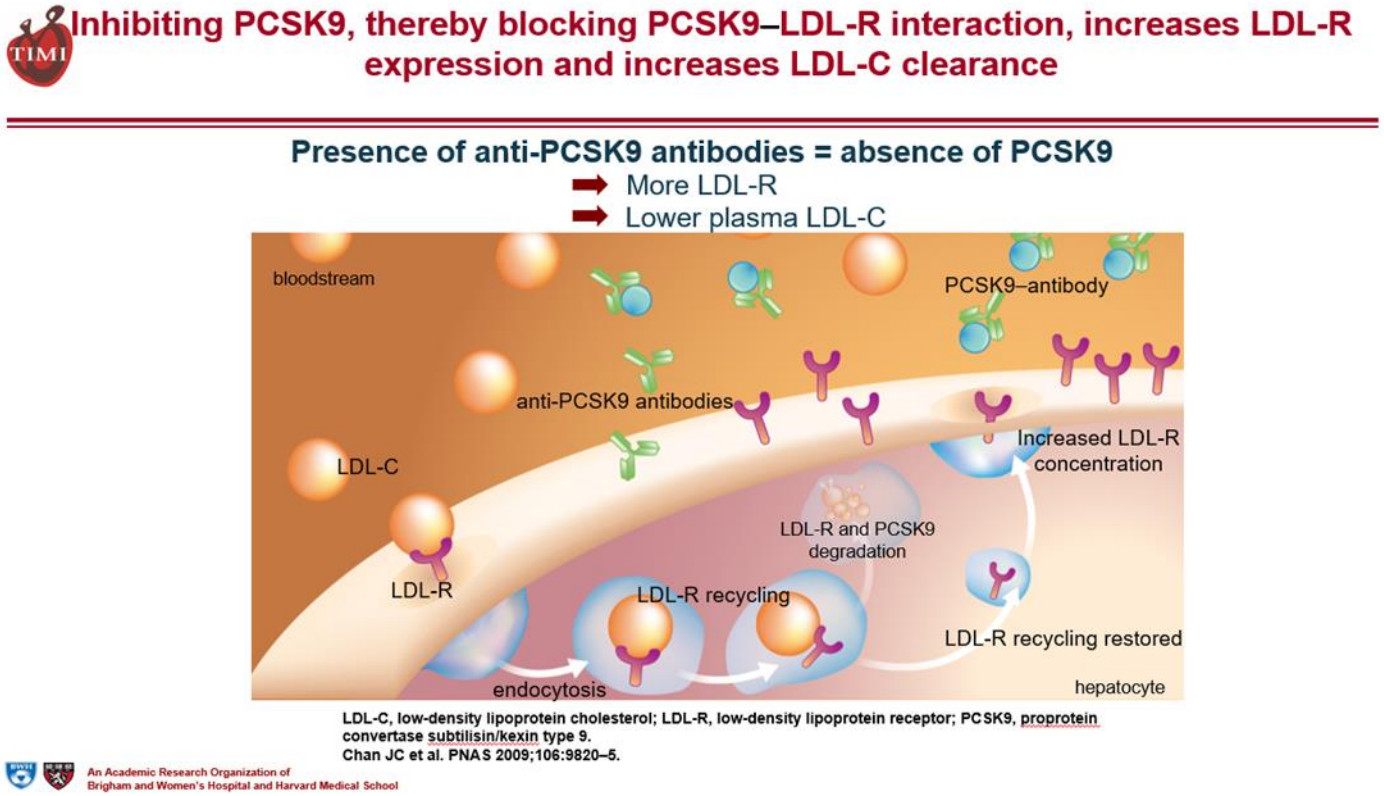
PCSK9 inhibitors

Mechanism of action

These drugs are subcutaneous injections containing fully human monoclonal antibodies against PCSK9, a protein which accelerates the degradation of the LDL receptor on the surface of the liver. They act as inhibitors to this protein, which increases the number of LDL receptors available to remove LDLc from the blood.



Appendices

Appendix 1 - An example of a suggested Lipid Optimisation in Secondary Prevention pathway

Appendix 2 - An example of a clinic set up - Staff Roles

Administration Support (0.2WTE)

- Booking clinic rooms
- Ensure Patient listed for CSN clinics (x2 per week) and Pharmacist clinic (x1 per week)
- Typing letters for Pharmacist clinic and sending out proformas for CSN clinics
- Point of contact for phone calls

Pharmacist (1 WTE)

- Lipid Optimisation clinic – number per week will depend on local demand and arrangements
- Admin support sessions and admin time to review blood results, arrange Homecare, following up patients to ensure meeting non-HDLc target <20% decline following initiation of medication
- 3-4 days in the community
    - Running GP IT systems searches for high lipids, family history
    - Inviting patients to Lipid Optimisation clinics

Skills identified	**Delivery**
Identification of lipid lowering compliance issues, signposting GP to alternatives (NEELI)	Teaching session
Definition of statin intolerance	
Interpretation of lipid profiles, able to request blood tests	
Awareness of NICE TA relating to Ezetimibe, Bempedoic Acid, Inclisiran and PCSK9i	
Awareness of mode of action LLT	
Aware how to monitor LLT treatments	
Able to initiate homecare arrangement (if required)	
Able to train patient to use PCSK9i	
Highlight benefits of lipid lowering therapy where required	Teaching session
Record PCSK9i initiation document	?use of proforma
Awareness of metrics to collect	
Interpretation of results	
Completion/dictation of letters	
Awareness of Familial Hypercholesterolaemia/FH criteria (?referral to lipid clinic)	Teaching session

Community/PCN Pharmacist role

Search for patients

Questions
-Compliance with medication?
-Take at morning/at night
-how to recall patient
-record this in the notes
-options to intensify –E10mg, Rosuva 20mg
-clinic locations GP v remote
-link into CVD prevent

Engage with practice/PCN

Describe approach
Describe medications
Describe project
Permission to work in practice
Space to see any patients/telephone follow up
Location of PCSK9i clinic

System 1 & EMIS searches

Search criteria

- Non HDLc ≥4mmol/L
- Previous
- Previous Stroke/TIA
- Previous PVD
- Previous angioplasty
- Previous unstable angina

Patient approach

?telephone approach
-taking medication/issues or not –if issues suggest alternative
-interested in PCSK9i or not?
-letter/info as follow up
-arrange to see

→**TC >7.5 = need full lipid profile ?diabetic - discuss with Lipid Clinic ?FH –may need letter to GP**

Admin role

Which clinics to book, where, how often
Which notes to pull
Outcome forms

Secondary Care Pathway

Cardiac SN obtains list of post ACS patients and these are listed for a clinic >3months post ACS. [*who sets up the clinic, sends out the requests?]*
8 patients in each clinic*, notes requested by Admin support*
Proforma completed, bloods taken
If statin intolerance signpost FATS
Bloods results reviewed
Template Letters dependent on lipid results

Appendix 3

Evolocumab Homecare registration and prescription	 120419 Repatha Registration Form.do  repatha prescription.doc
Alirocumab Homecare registration and prescription	 SAGB.ALI.16.10.093 4(2) Prescription Tem  SAGB.ALI.17.07.091 8aj(2) Praluent Regis
Newcastle PCSK9i record sheet	 PCSK9 Inhibitor Record Sheet Dec 20
HEART UK PCSK9i patient information leaflet	 pcsk9i-factsheet heart uk.pdf