NHS
North Yorkshire & York Area Prescribing Committee

North Yorkshire and York Lipid Treatment Guidance

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Lipid management pathway for patients with CVD and risks of CVD

Shared Decision Making
Outline the risks and benefits of statin treatment, taking into account lifestyle modifications, comorbidities, polypharmacy, general frailty and life expectancy.
QRISK3 is the current version of the QRISK calculator. www.qrisk.org/three
Lifestyle to be considered fundamental to this guidance. Lifestyle helps to reduce future CVD risk. Statins are effective at reducing cholesterol. Both important.

Primary Prevention

CKD 3 and above (regardless of cholesterol level or risk of CVD) QRISK >10% 10-year cardiovascular risk
Type 1 diabetics older than 40 or nephropathy or had T1DM for more than 10 years or other CVD risk factors

Recommended
Atorvastatin 40mg

Secondary Prevention

Established CHD/IHD/MI Ischemic Stroke & TIA,PAD

Recommended
Atorvastatin 80mg

Second Line (those intolerant to Atorvastatin)
Initiate one month of Rosuvastatin 5 mg once daily (doubled to 10 mg daily for primary prevention on repeat prescription after one month if no reported side effects). For secondary prevention up to 40 mg once daily, dose to be increased gradually at intervals of at least 4 weeks. (Avoid 40mg dose in Asian population)

Aim for Total cholesterol <4mmol/l or >40% reduction in baseline non-high-density lipoprotein (non-HDL) with up titration to 80mg Atorvastatin or alternative statin if required

- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value and/or non-HDL-C < 2.5mmol/L after 3 months consider adding Ezetimibe 10mg OD (NICE TA385)
- If recommended statin treatment is contraindicated or not tolerated then:
  - 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) – see appendix 2

Before starting lipid modification therapy take full lipid profile and check ALT, rule out 2ºcauses such as hypothyroidism and nephrotic syndrome.

Total / HDL / non-HDL / triglycerides.
A fasting sample is not needed

Repeat lipid profile and ALT after 3 months

Show patients targets /progress to help behaviour

If target not achieved discuss adherence / understanding and timing of dose / diet and lifestyle, Consider increasing dose of statin.

Recommend inclisiran alone OR in combination with lipid-lowering therapies:
Low density lipoprotein cholesterol **(LDL-C)** concentrations are **persistently 2.6 mmol/l** or more, despite maximum tolerated lipid lowering therapy. (NICE TA733) – see appendix 3

Check ALTs at baseline and at 3 months. No further checks required after starting statin unless clinical concern (e.g. liver disease).
Advise women to stop taking statin if pregnant or 3 months before attempting to conceive.

Please consider
Familial hypercholesterolaemia and hyperlipidaemia in anyone with atotal cholesterol >7.5mmol/L or LDL >4.9 mmol/l. Talk to patients to get family history
See pathway for further information about the above.

Appendix 1 Lipid Guidance: Supporting Clinical Information

Definition

Patient has an abnormal lipid profile or is being treated because they are considered to be at high risk of or have existing cardiovascular disease.

Cardiovascular disease includes angina, heart attack, stroke, TIA and peripheral vascular disease.

Exclude the following

- People under 16
- People who are allergic to statins
- People with an estimated life expectancy of less than 2 years
- Statins are contraindicated in pregnancy and should be discontinued 3 months before pregnancy and restarted after breastfeeding has finished.

General points

- High cholesterol causes cardiovascular disease and accounts for a third of all heart attacks.
- Lifestyle change is key to cholesterol lowering. Where this is ineffective or in people at highest risk (e.g. pre-existing CVD or familial hypercholesterolaemia (FH)), drug therapy with statins and other medications is very effective.
- Every 1mmol/l reduction in low-density lipoproteins (LDL) cholesterol reduces risk of a cardiovascular event by 25%

  (Ref Lancet, 2016, Interpretation of the evidence for the efficacy and safety of statin therapy, Collins et al)
- People with high cholesterol who also have other risk factors (e.g. high blood pressure, diabetes, smoking) are at significantly greater risk of CVD and have most to gain from a reduction in cholesterol.

Management guidelines

- Management of lipids should be in the context of a formal risk assessment made using QRISK3 or JBS3 and medication started in the context of risk reduction according to the patients informed opinion.
- Cardiovascular risk assessment tools should not be used in people with Type 1 diabetes, CKD with eGFR <60ml/min/1.73m2, known Familial Hyperlipidaemia and existing CVD.
- Lifestyle advice in the context of weight optimisation, diet, physical activity, smoking cessation are an integral part of the consultation; however for the majority, a low-fat diet will have only a minor (<10%) effect on lipid levels.
- Improving diabetes control and reducing alcohol intake should be a target for management.
- NICE Guidelines do not recommend the use of fibrates, omega 3 fatty acids, plant stanols or sterols in the context of cardiovascular risk reduction.

Use of statins for cardiovascular risk reduction

- As a class, statins are the most highly studied therapy and have revolutionised the prevention and management of cardiovascular disease.
- NICE Guidance recommends the use of a high-intensity statin when the decision has been made with the patient to use medication.
- NICE guidance recommends the use of atorvastatin for those estimated to be at >10% ten-year risk, people with CKD, those over the age of 40 with type1 diabetes, people with type 2 diabetes over 10% risk, and those with established cardiovascular disease.
- North Yorkshire and York APC recommendation:

  Secondary Prevention = 80mg of atorvastatin

  Primary prevention = 40mg of atorvastatin

  - Use a lower dose of Atorvastatin if there is a potential drug interaction, high risk of experiencing adverse effects, or patient preference.
  - Offer Atorvastatin 20mg if CKD (people with GFR< 60 mL/min/1.73m2).

Follow up and potential complications of treatment

- It is important to discuss the risks and benefits of statin therapy and individualise the advice
- Community pharmacists can offer support when new prescriptions are issued in the form of the New Medicines Service.
- NICE guidance recommends follow up at 3 months after commencing a statin, with lipid profile and liver enzymes (ALT). This does not need repeating unless dose has increased or kidney function has declined.
- If the target of > 40% non-HDL lowering is not achieved:
  - Discuss adherence
  - Optimise diet and lifestyle measures (including alcohol intake)
  - Consider increasing the dose if taking less than atorvastatin 80mg and at high risk
- If statin is not tolerated, follow **statin intolerance pathway** and consider alternative lipid lowering medicines such as ezetimibe etc in line with the **treatment pathway**.

Shared decision-making resources

Benefits per 10,000 people taking statin for 5 years	Events avoided
Avoidance of major CVD events in patients with pre-existing CVD & a 2mmol/l reduction in LDL	1000
Avoidance of major CVD events in patients with no pre-existing CVD & a 2mmol/l reduction in LDL	500

Adverse events per 10,000 people taking statin for 5 years	Adverse events
Myopathy	5
Haemorrhagic Strokes	5-10
Diabetes Cases	50-100

Links

- BHF information on statins
- Heart UK: Information on statins
- NICE shared decision-making guide

Statin Intensity table

	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%**	**48%**	**55%**
Rosuvastatin	**38%**	**43%**	**48%**	**53%**	
Atorvastatin + Ezetimibe		**52%**	**54%**	**57%**	**61%**
Ezetimibe	**19%**				
Bempedoic Acid	**23%**				
Inclisiran	**52%**				
PCSKis	**60%**				

Low intensity statins

Medium intensity statins

High intensity statins

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

Appendix 2: Bempedoic acid in management of hyperlipidemia

Indications (in line with NICE TA694)

Use as an adjunct to diet.
In combination with ezetimibe: in patients who are either statin intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone.
Prior to prescribing bempedoic acid, consider whether alternative agent would be more appropriate such as PCSK9 inhibitor (see Appendix 1 for PCSK9 inhibitor pathway/ eligibility: NICE TA393/394).

Formulations

Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination. Try addition of bempedoic acid (Nilemdo) with ezetimibe. If tolerated switch to combination therapy (Nustendi). Note Nilemdo and Nustendi cost the same (£55.44/ 28 tablets).

Dosage

Bempedoic acid 180 mg OD (Nilemdo)
Bempedoic acid and ezetimibe 180mg/10mg once daily (Nustendi).

Special populations

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. There are limited data available in patients with severe renal impairment eGFR < 30 mL/min/1.73 m2, and patients with end-stage renal disease (ESRD) on dialysis have not been studied.

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A). It is not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment.

History of Gout: Increased serum uric acid

- Gout was reported in 1.5% of patients treated with bempedoic acid and 0.4% of patients treated with placebo.
- Increase in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment.
- The risk for gout events was higher in patients with a prior history of gout (11.2% bempedoic acid versus 1.7% placebo).
- Treatment with bempedoic acid should be discontinued if hyperuricaemia accompanied with symptoms of gout appear.

Paediatric population
The safety and efficacy of bempedoic acid in children aged less than 18 years have not yet been established.

Pregnant and lactating women
There are no available data on bempedoic acid use in pregnant or lactating women to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Elderly
No dose adjustment is necessary in elderly patients.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy
- Breast-feeding
- Concomitant use with simvastatin 40 mg OD or higher dose.

Drug interactions

Simvastatin	Concomitant use of bempedoic acid causes an increase in statin concentration and may increase the risk of statin related myopathy	Avoid concomitant use with simvastatin dose greater than 20 mg
Pravastatin		Avoid concomitant use with pravastatin greater than 40 mg

Statin Intolerance

Definition

- Presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy. OR Any adverse event (AEs) considered unacceptable by the patient, and/or some laboratory abnormalities, both attributed to statin treatment and leading to its discontinuation.
- Statin-associated muscle symptoms (SAMS) are one of the principal reasons for statin non-adherence and/or discontinuation. However, not all such symptoms should lead to a label of 'statin intolerance' as they may not be truly statin related muscle toxicity (SRM) as demonstrated by resolution on de-challenge and recurrence with re-challenge.
- Non-statin related musculoskeletal symptoms (non-SRM): If patients report symptoms that are not typical of SRM (e.g. asymmetric distribution, failure to resolve with de-challenge despite normal CK) then consider other musculoskeletal disorders, metabolic, degenerative or inflammatory e.g. Vitamin D deficiency, polymyalgia rheumatica. Check bone profile, Vit D, CRP.
- Please follow the weblink below for full NICE guidance for further management of statin intolerance

Other special warnings and precautions for use

Tendon Rupture

- Bempedoic acid use is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.5% of patients treated with bempedoic acid involved the rotator cuff, biceps tendon or Achilles tendon.
- Discontinue bempedoic acid immediately if the patient experiences rupture of a tendon.
- Consider discontinuing bempedoic acid if the patient experiences joint pain, swelling or inflammation. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.

Elevated liver enzymes

- In clinical trials, elevations of > 3× ULN in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported with bempedoic acid in 0.7% compared to 0.2% in placebo.
- Treatment with bempedoic acid should be discontinued if an increase in transaminases of > 3× ULN persists.

Decreased haemoglobin

- Decrease in haemoglobin was observed in clinical trials with bempedoic acid. In the pooled placebo-controlled trials, a decrease in haemoglobin from baseline of ≥ 20 g/L and < lower limit of normal (LLN) was observed in 4.6% of patients in the bempedoic acid group compared with 1.9% of patients on placebo.
- The decreases in haemoglobin usually occurred within the first 4 weeks of treatment and returned to baseline following discontinuation of treatment.

Cautions

- Age ≤ 18 yrs
- Patients with hyperuricemia or history of gout
- CKD stage 4 and 5
- Patients with severe hepatic impairment
- Allergy or hypersensitivity to any excipients/ active substance
- Pregnant and lactating women.

Patient counselling information

Risk of Hyperuricemia
Advise patients of the risk of elevated serum uric acid levels, including development of gout. Inform patients that serum uric acid levels may be monitored during treatment with bempedoic acid. Patients with signs or symptoms of hyperuricemia should contact their healthcare provider if symptoms occur.

Risk of Tendon Rupture
Inform patients of the risk of tendon rupture. Advise patients to rest at the first sign of tendinitis or tendon rupture and to immediately contact their GP if tendinitis or tendon rupture symptoms occur.

Pregnancy
Advise women of child-bearing age about the potential risk to foetus, and the need to inform their healthcare provider of a known or planned pregnancy.

Monitoring (Baseline and 12 weeks post initiation):

- Haemoglobin
- Serum uric acid, liver function, renal function, lipid profile including LDL, creatinine kinase.

If patient develops adverse effects discontinue the medication and seek alternative or refer to lipid clinic.

References

1) Bempedoic acid with ezetimibe for treating primary hypercholesterolemia or mixed dyslipidaemia technology appraisal guidance [TA694] Published date: 28 April 2021 https://www.nice.org.uk/guidance/ta694/chapter/2-Information-about-bempedoic-

2) ReKausik K. Ray, Harold E Bays et al. Safety and Efficacy of Bempedoic Acid to reduce cholesterol N Engl J Med 2019 Mar 14; 380(11):1022-1032.

3) Goldberg AC, Leiter LA, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease. JAMA 2019 Nov 12; (18): 1780-1788.doi: 10.1001/jama.2019.16585.

4) Christie M Ballantyne, Maciej Banach et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia. Atherosclerosis 2018 Oct; 277:195-203. doi: 10.1016/j.atherosclerosis.2018.06.002. Epub 2018 Jun 12.

5) Highlights of prescribing information Nexletol™ safely and effectively. (Bempedoic acid) tablets, for oral use Initial U.S. Approval: 2020, Reference ID: 4564667.

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

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

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

Appendix 3: Inclisiran in management of hyperlipidemia

Indications (in line with NICE TA 733)

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:
  - 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 2.6mmol/l or more, despite maximum tolerated lipid-lowering therapy, **and**
- Inclisiran is recommended only in research for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in adults who have no history of cardiovascular events. This research is in the form of a clinical trial currently in development.

Presentation

Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution

Dosage

284 mg inclisiran administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.

Special populations

Elderly
In the clinical trials, no differences in safety were shown between older (65 years of age or older) and younger subjects.

Body weight, gender and ethnicity
Body weight, gender and race were not found to significantly influence the pharmacodynamics of inclisiran.

Hepatic and renal function
The manufacturer recommends that no dose adjustment is necessary in patients with mild, moderate or severe renal impairment. The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after dosing.
No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Inclisiran has not been studied in patients with severe hepatic impairment.

Pregnancy
There is no safety data on using inclisiran during pregnancy. For this reason, inclisiran is best avoided during pregnancy.

Breastfeeding
It is unknown whether inclisiran is excreted in human milk. Pharmacodynamic/toxicological data in animals have shown excretion of inclisiran in milk. A risk to newborns/infants cannot

be excluded. A risk benefit decision needs to be made with the mother as to whether to discontinue/abstain from inclisiran therapy or to discontinue breastfeeding

Drug interactions

Inclisiran is not expected to have clinically significant interactions with other medicinal products.

Product storage and administration

- Inclisiran does not require any special storage conditions. It should not be frozen.
- Inclisiran has a 2-year shelf life
- Inclisiran solution should be clear, colourless to pale yellow and essentially free of particulates. If the solution contains visible particulate matter, the solution should not be used.

What monitoring is required?

Reporting suspected adverse reactions is important as it allows continued monitoring of the benefit/risk balance. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

There are no additional monitoring requirements for inclisiran for patients with reduced renal or hepatic function.

Following initiation, cholesterol monitoring and adherence to medication should be in line with local lipid management guidelines.

How is stock ordered and supplied?

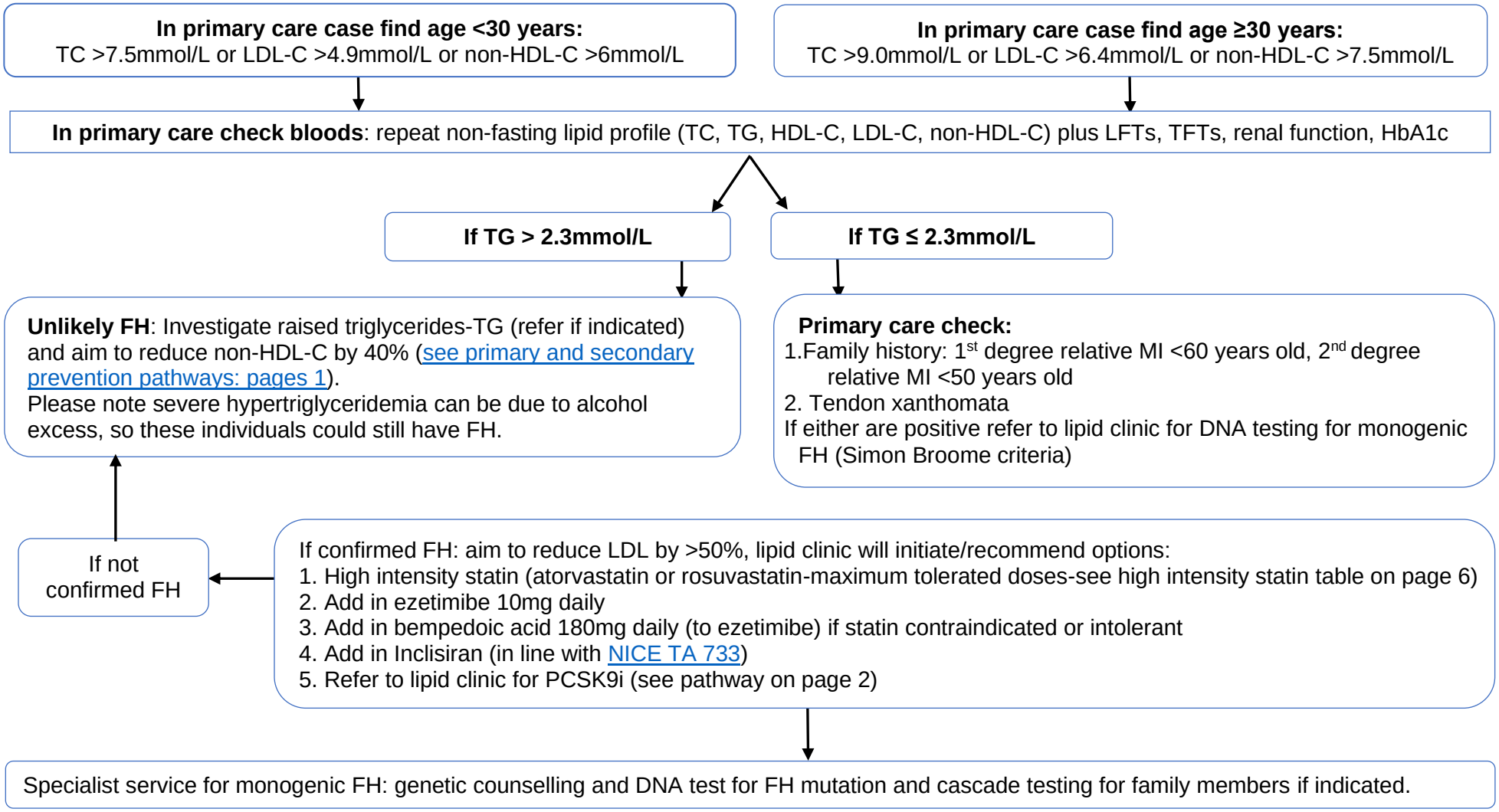
The preference is for primary care to purchase stock from the wholesaler (AAH), and then to make a claim on the monthly submitted FP34D. Typically, there would be no patient prescription charge via this method.

Inclisiran can also be supplied by the FP10 route, with the patient bringing the injection to the surgery for administration. If issued via FP10, patients would pay the prescription charge, if they normally do so.

References

1) NICE TA733: Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia. Published October 2021. https://www.nice.org.uk/guidance/TA733
2) NHS England. Lipid Management - Rapid Uptake Product. Accessed July 2021. https://www.england.nhs.uk/aac/what-we-do/what-innovations-do-we-support/rapid-uptake-products/lipid management/
3) Stoekenbroek RM et al. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. Future Cardiol 2018;14(6):433-442. https://doi.org/10.2217/fca-2018-0067
4) Summary of Product Characteristics - Leqvio. Novartis. Last updated December 2020. https://www.medicines.org.uk/emc/product/12039
5) Ray KK et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. N Engl J Med 2020; 382: 1507-1519. https://www.nejm.org/doi/full/10.1056/NEJMoa1912387
6) Raal FJ et al. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. N Engl J Med 2020; 382:1520-1530. https://www.nejm.org/doi/full/10.1056/NEJMoa1913805
7) Ray KK et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. Trial Protocol for Orion 10 and 11 trials. N Engl J Med 2020;382(16):1507-1519. Supplementary Material). Available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1912387/suppl_file/nejmoa1912387_protocol.pdf
8) Ray KK et al. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. Supplementary Appendix for Orion 10 and 11 trials. N Engl J Med 2020; 382:1507-1519 (Supplementary Material). Available at https://www.nejm.org/doi/suppl/10.1056/NEJMoa1912387/suppl_file/nejmoa1912387_appendix.pdf

Appendix 4: Familial Hypercholesterolaemia (FH) Case Finding Pathway



Appendix 5: Recommended Criteria for Referral to Lipid Clinic

Hospital lipid clinic	Referral Criteria
Severe hypercholesterolaemia	Cholesterol >9.0 mmol/L (or non HDL-C > 7.5 mmol/L) regardless of existing heart disease / family history
Suspected familial hypercholesterolaemia (FH)	Cholesterol>7.5 mmol/L and LDL-C >4.9 mmol/L AND • Premature CVD (age <60yrs) in the patient OR • Family history: 1st degree relative MI < 60 years old , 2nd degree relative MI <50 years old OR • Presence of tendon xanthomata
Family screening	Cascade screening from identified patient with familial hypercholesterolaemia with a genetic diagnosis of FH
Severe Hypertriglyceridemia	• Triglyceride > 20 mmol/L OR • Triglyceride 10 -20 mmol/L which persists on a fasting lipid profile (2 samples 1 week apart) OR • Triglyceride 4.5 -9.9 mmol/L WITH non-HDL cholesterol > 7.5 mmol/L
Secondary prevention of CVD	• Unable to meet target reductions in LDL-C or non HDL-C despite maximal doses of statins and other lipid lowering medications.
Statin intolerance	• Intolerance of 3 or more statins

Appendix 6: Pathway for consideration of PCSK9 Inhibitors. NICE TA393/TA394

(PCSK9 Inhibitors: Secondary care only)