DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

IDENTIFICATION & MANAGEMENT OF FAMILIAL HYPERCHOLESTEROLAEMIA

(Based on NICE clinical guideline 71, last updated Oct 2019)

- Do not use CHD risk estimation tools e.g., QRISK2 because people with FH are already at a high risk of premature CHD

- All patients with FH should be offered a referral to a lipidologist for confirmation diagnosis of familial hypercholesterolaemia (homozygous and heterozygous)

- NICE recommends offering a high-intensity statin to achieve >50% reduction in LDL-C from baseline. 1st line atorvastatin 20mg (local specialist advice that 10mg atorvastatin may be an appropriate starting dose as a way to titrate up to limit adverse effects and some patients obtain good response with 10mg dosage).

- Check baseline lipids, LFT & CK before and 3 months after starting treatment.

- Treatment should be titrated up and optimized if treatment target not met following 1st line atorvastatin 20mg. Rosuvastatin may be considered as alternative treatment option.

- Compliance with medication should be checked at every stage of management change.

- Patients not able to tolerate one statin may benefit from a trial with another. Alternatives include atorvastatin 10mg, simvastatin 10mg, pravastatin 10mg (titrating up to 40mg), and rosuvastatin 5mg. (See appendix 1 statin intensity)

- Patients unable to tolerate all generic statins (simvastatin, atorvastatin, pravastatin, rosuvastatin) should be referred back to a lipidologist

- Ezetimibe is a monotherapy treatment option in patients truly intolerant to statins. Ezetimibe in combination with a statin is a limited treatment option following intensification of statins. (NICE TA385)

- Bempedoic acid with ezetimibe (NICE TA694) is a treatment option if statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-c well enough. Monitor LFT at baseline, 3 &12 months.

- Most patients will be managed in primary care but re-referral back to the lipidologist is appropriate if cascade screening has not been undertaken or diagnosis is in doubt; or if LDL-c cannot be reduced by at least 50% despite treatment optimization in primary care. Specialist may consider other treatment options including PCSK9 alirocumab and evolocumab in accordance with NICE TA393 and TA394.

1. Diagnosis

NICE makes a recommendation to systematically search primary care records for people who are at highest risk of FH as defined below:

- younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l **and**
- 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/l

For people with a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative), but whose total cholesterol is unknown, offer to measure their total cholesterol.

- Suspect FH in adults who have total cholesterol concentrations greater than 7.5 mmol/l and/or in the presence of a personal or family history of premature coronary heart disease (an event before 60 years in an index individual or first-degree relative).
- The probability of FH increase with higher LDL-c. It is unusual for triglycerides to be significantly raised; if the triglycerides are raised, consider advice and guidance request or referral to a local lipid clinic to clarify diagnosis.
- Exclude secondary causes of hypercholesterolaemia before considering a diagnosis of FH, such as hypothyroidism.
- Use the **Simon Broome criteria** to make a diagnosis of FH.
- Absence of clinical signs (for example, tendon xanthomata) does not exclude a diagnosis of FH.
- To confirm a diagnosis of FH, take at least two measurements low-density lipoprotein cholesterol (LDL-c) concentration. Measurement of fasting lipid profiles is required and allows measurement of plasma triglyceride concentrations, which is important to exclude a mixed hyperlipidaemia. It is perfectly acceptable to accept a random lipid profile as the first test, and if levels are significantly raised do a second test as a fasting test.
- When considering a diagnosis of FH, always take a family history with particular reference to premature CVD. However, a family history may have confounders (e.g., adoption, non-paternity, early death from other causes) and its absence does not exclude the diagnosis.

Simon Broome diagnostic criteria for index individuals

Diagnose a person with **definite** FH if they have:

- cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative
- **Or** DNA-based evidence of an LDL-c receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Diagnose a person with **possible** FH if they have cholesterol concentrations as defined in table 1 **and** at least one of the following:

- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.
- Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

Table 1 Cholesterol levels to be used as diagnostic criteria for the index individual[1]

	Total cholesterol	LDL-c
Child/young person	>6.7 mmol/l	>4.0 mmol/l
Adult	>7.5 mmol/l	>4.9 mmol/l

[1]Levels either pre-treatment or highest on treatment

2. Management

Before Starting

- Do not use coronary heart disease risk estimation tools (eg QRisk2) because people with FH are already at a high risk of premature coronary heart disease.
- Ensure baseline lipids, LFT, and CK result available. A baseline resting ECG is recommended for adults.
- Regard lifestyle advice as a component of medical management and not as a substitute for lipid-modifying drug therapy. The five key elements are stopping smoking, diet, physical activity, weight management, and alcohol consumption.
- Inform patient that lipid-modifying drug treatment is life-long.

How to treat

- NICE recommends offering a high-intensity statin to achieve >50% reduction in LDL-C from baseline.
- 1st line atorvastatin 20mg (local specialist advice that 10mg atorvastatin may be an appropriate starting dose as a way to titrate up to limit adverse effects and some patients obtain good response with 10mg dosage).
- Where atorvastatin 10-20mg does not achieve this, increasing to atorvastatin 40-80 mg will be necessary for these patients.
- Alternatives high intensity statin including rosuvastatin 10mg.
- Ezetimibe (**Grey** as per NICE TA385)
  - Monotherapy is a treatment option in patients contraindicated or unable to tolerate all statins.
  - In combination with a statin is a limited treatment option following intensification of statins in patients where lipid level are not adequately controlled and changing from the initial statin (atorvastatin) is being considered.
- Bempedoic acid (Grey as per NICE TA694) is an option if statins are not tolerated or contraindicated, and ezetimibe alone does not control low-density lipoprotein cholesterol well enough. Bempedoic acid can cause hepatic enzyme changes/ hyperuricaemia- Manufacturer advises discontinue treatment if transaminase levels at least 3 times the upper limit of normal and persist; or in hyperuricaemia accompanied with symptoms of gout. Monitor LFT at baseline and at 3 &12 months.
- Treat these patients with blood pressure lowering medication (target BP <140/85 mmHg)
  - adults over 40 years of age with sustained systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg
  - adults 40 years of age or younger if they have sustained systolic BP $\geq$ 160 mmHg and/or diastolic BP $\geq$ 100 mmHg.
- When treatment fails to improve LDL-c always check compliance, revisit lifestyle modification advice, recheck for secondary causes of hyperlipidaemia and stop medications that are having no benefit (especially rosuvastatin or ezetimibe).

Intolerance to statin

Intolerance is defined as *the presence of clinically significant adverse effects that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised*. Adverse effects include evidence of new-onset muscle pain (often associated with levels of muscle enzymes in the blood indicative of muscle damage), significant gastrointestinal disturbance or alterations of liver function tests.

- Some patients intolerant of simvastatin and atorvastatin are able to tolerate pravastatin. Pravastatin although less potent in reducing LDL-c is still effective and remains a treatment option in some patients
- Published data in a very small patient group supports infrequent dosing (i.e., less than once daily) of atorvastatin or rosuvastatin in patients otherwise intolerant of statins. The dosing of atorvastatin or rosuvastatin in this manner should only be initiated in a specialist lipid clinic but can then be continued in primary care.

Rosuvastatin –

Rosuvastatin (**Grey** 2nd line to atorvastatin for FH) may be considered in patients with:

Complete intolerance of 1st line choice atorvastatin due to myalgia. Less than once daily dosing strategy may be adopted (e.g. atorvastatin 10mg every other day). Rosuvastatin to be prescribed initially 5mg less than daily and titrated to 5mg daily if possible. Tolerance of higher doses is not likely but can be tried.

OR

Partial tolerance of other statins at low-moderate doses (simvastatin 40mg, pravastatin 40mg and atorvastatin 20mg max tolerated dose) but not reaching LDL-C target. In these patients it is appropriate to commence rosuvastatin with titration to maximum tolerated/ minimum necessary dose to achieve 50% reduction in LDL-c (dose range 5mg-40 mg daily).

- A start dose of 5 mg is recommended in patients >70 years and for patients of Asian ancestry. The 40 mg dose is contraindicated in patients of Asian ancestry.
- No dose adjustment is necessary in patients with mild to moderate renal impairment. The recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment (creatinine clearance of <30 ml/min) is contraindicated for all doses
- An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Other Specialist options for LDL- C control

- Bile acid sequestrants colestyramine- but this is often not tolerated.
- Fibrates may be used in people intolerant of statin/ ezetimibe, only if triglycerides above normal, or on specialist advice. Patient should be re-assessed at 3 months and treatment discontinued if no improvement. Fenofibrate is the preferred choice. Ciprofibrate has been locally classified as Do Not Prescribe (DNP) as less cost effective.

Inclisiran (JAPC classification RED as per NICE TA733)

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.

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.

PCSK9 inhibitors- alirocumab and evolocumab (JAPC classification RED)

NICE TA393 and TA394 recommends alirocumab and evolocumab as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia in **selected patients** after statin/ ezetimibe treatment have been optimised. They are **only recommended by lipid specialist and are supplied through hospital via homecare**; GPs may be asked to prescribe statin in conjunction.

Ensure treatment is optimised before considering referral to lipid specialist for consideration of inclisiran or PCSK9 inhibitors.

Low-density lipoprotein cholesterol concentrations above which alirocumab/evolocumab are recommended (NICE TA393/394)

	Without CVD	**With CVD**
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

See appendix 2 Treatment algorithm for FH

3. Follow up

- Patients should be reviewed annually for assessment of: lipids, concordance with treatment, control of other risk factors, new symptoms of cardiovascular disease and progress with family (cascade) testing.
- Most patients will be managed directly in primary care under the guidance of a lipidologist. Specialist re-referral is indicated if;
  - LDL-C cannot be reduced by at least 50% despite treatment optimisation in primary care
  - Cascade screening is necessary (all newly diagnosed cases of FH or cases in whom cascade screening has not been performed)
  - Diagnosis is in doubt (e.g., presence of raised plasma triglyceride concentrations)
  - Pregnancy is being considered.
  - SE compromising concordance with lipid modifying therapy
  - Unable to tolerate all generic statins

4. Special considerations

Women with familial hypercholesterolaemia

- Refer to a specialist lipid clinic if pregnancy being considered or if the woman is pregnant.

Children and young people

- Refer children and young people to a specialist with expertise in familial hypercholesterolaemia in this age group and in an appropriate setting. This would indicate a paediatrician with a metabolic clinic, rather than an adult lipid clinic.
- In children at risk of familial hypercholesterolaemia because of an affected parent, consider a DNA test by the age of 10 years if the family mutation is known; otherwise measure low density lipoprotein
- The Simon Broome criteria are NOT applicable to relatives of known FH carriers as the prior probability is high (50%). Use appropriate age and sex-related charts published by NICE.
- For children with FH treatment with a statin may be appropriate from the age of 10 years (where licensed), but should be initiated by a specialist following an individualised assessment
- Routinely monitor growth and pubertal development in children and young people.

References

- Identification and management of familial hypercholesterolaemia NICE Clinical Guideline 71, August 2008- last updated October 2019 https://www.nice.org.uk/guidance/cg71 [accessed Sept 202]
- NICE TA 385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (Febrary 2016) https://www.nice.org.uk/guidance/ta385 [accessed Oct 2019]
- NICE TA 393/394 Alirocumab/Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016) https://www.nice.org.uk/guidance/ta393(4) [accessed Oct 2019]
- SPC Rosuvastatin 10mg https://www.medicines.org.uk/emc/product/8872/smpc [accessed Oct 2019]

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Document control	Date
Add in bempedoic acid	July 2021
Addition of inclisiran as per NICE TA733	October 2021

Appendix 1 - statin intensity (as defined by NICE CG181)

20-30%	**Low intensity**
30-40%	**Medium intensity**
Above 40%	**High intensity**

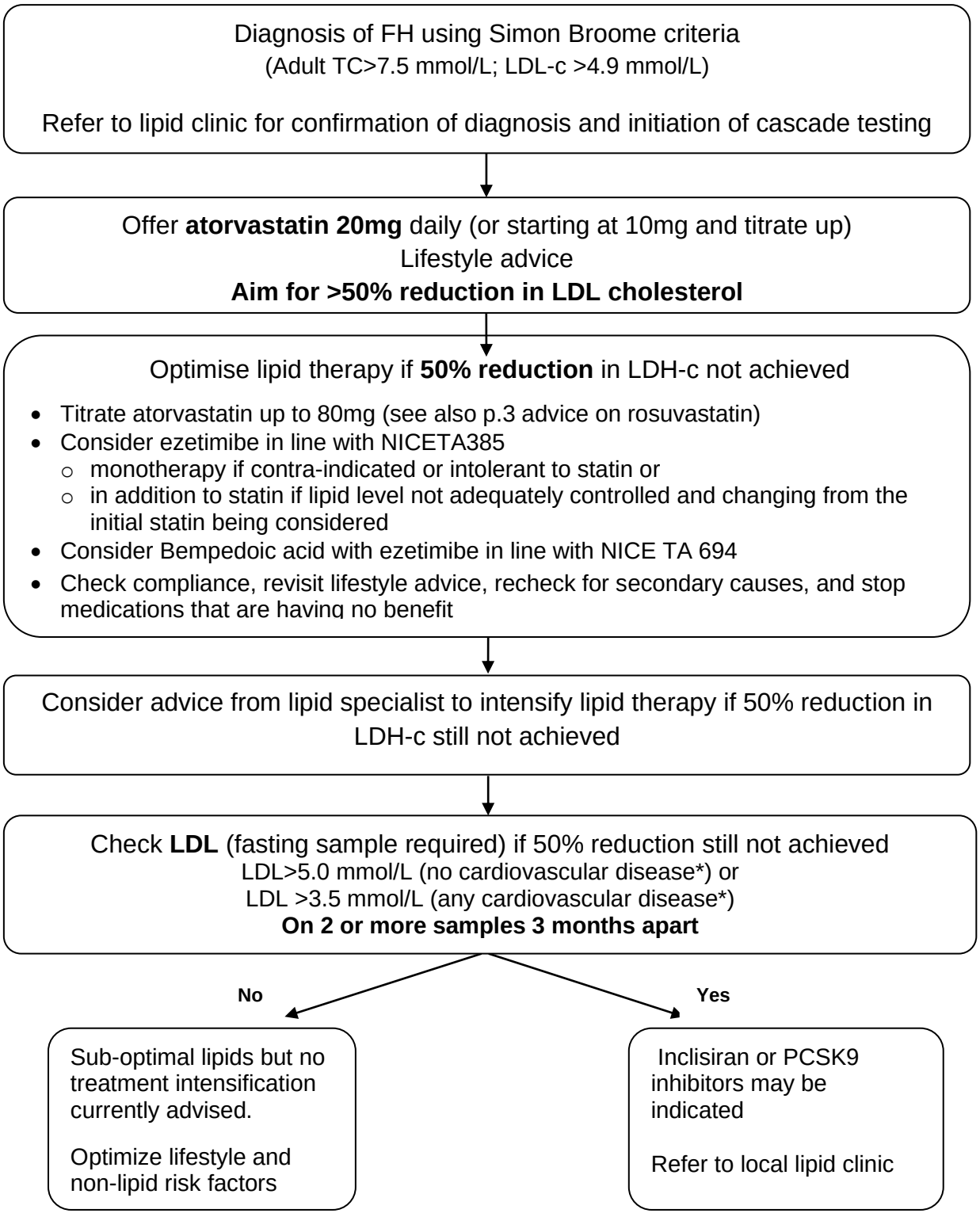
Drug	Daily dose (mg)				
	5	**10**	**20**	**40**	**80**
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	**42%***
Atorvastatin		37%	**43%**	**49%**	**55%**
Rosuvastatin	38%	**43%**	**48%**	**53%**	-

% = percentage reduction in LDL cholesterol

***Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80mg) simvastatin. This dose should only be considered in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

This table is based on: Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326: 1423.

Appendix 2 - Treatment algorithm for FH



* defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, peripheral arterial disease.