Hull University Teaching Hospitals NHS Trust

# CVD Risk Optimisation and Lipid Lowering Therapy Guideline

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## 720

Hull University Teaching Hospitals NHS Trust

## Document Control

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| **Document Managed by Title:** | Consultant Chemical Pathology and Metabolic medicine |
| **Contact details for further information:** | hyp-tr.policies@nhs.net |
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## Version Control

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|---|---|---|---|
| March 22 | V3 | D Narayanan | Full review and update post recent NICE TA |
| December 22 | V4 | D Narayanan | Changes to secondary CVD pathway post NICE TA 805 |
| April 24 | V5 | D Narayanan | Update to FH primary care pathway, Bempedoic acid drug status |

## 1. Summary

The lipid guideline is a comprehensive guideline on the management of patients with lipid disorders inclusive of Familial Hypercholesteroalemia (FH), and patients with primary and secondary prevention of cardiovascular disease.

## 2. Purpose, Legal Requirements and Background

The purpose of the document is to standardise the management of lipid disorders across Hull and East Riding region in primary and secondary care.

## 3. Responsibilities, Accountabilities and Duties

This guideline is applicable to all clinical staff involved in the management of lipids and cardiovascular risk reduction in Hull University Teaching Hospitals NHS Trust and Primary care networks within Hull and East Riding of Yorkshire.

## 4. Guideline Details

### CVD Risk Optimisation Tool Kit

Treatment targets and goals for CVD prevention:

| CVD Check List | Recommendation |
|---|---|
| Document Family history of premature heart disease | Premature heart disease is defined as onset <60 years in first degree relatives and <50 years in second degree relatives |
| Does the patient have Familial Hypercholesterolaemia? | Refer to Simon Broome criteria & flow chart for Familial Hypercholesterolaemia – Appendix A (page 13)<br>NICE CG71: https://www.nice.org.uk/guidance/cg71 |
| History of Chronic kidney disease? | Document stage of CKD, if applicable<br>https://www.nice.org.uk/guidance/ng203 |
| Diabetes | Type 1: https://www.nice.org.uk/guidance/ng17<br>Type 2: https://www.nice.org.uk/guidance/ng28<br>Target HbA1c level of 53 mmol/mol |
| Smoking | Avoid exposure to tobacco in any form<br>https://www.nice.org.uk/guidance/ng209/<br>Overview \| Tobacco: preventing uptake, promoting quitting and treating dependence \| Guidance \| NICE<br>Refer to stop smoking service locally in Hull |
| Blood pressure | https://www.nice.org.uk/guidance/ng136<br>Target: <140/90 mm Hg (if primary prevention and not known to have documented hypertension, pregnancy, diabetes or chronic kidney disease). |

| | |
|---|---|
| | Offer Ambulatory BP if clinic BP between 140/90 mmHg and 180/120 mmHg.<br>Diabetes:<br>In patients with type 1 Diabetes: target <135/85 mmHg<br>In patients with type 1 Diabetes and end organ involvement: target <130/80 mmHg<br>In patients with type 2 Diabetes: target <135/85 mmHg<br>Chronic kidney disease:<br>In adults with CKD and an ACR of >70 mg/mmol: target < 130/80 mmHg |
| Lipids | Primary prevention of CVD: Appendix B (page 15)<br>Target for High risk CVD (see list below) patients: >40% reduction in Non- HDL-C from baseline<br>Secondary prevention of CVD: Appendix C (page 16)<br>Target: LDL-C goal of ≤ 1.8 mmol/L<br>Statin Intolerance pathway: Appendix D (page 17) |
| Alcohol | <14 Units per week |
| Body weight | Healthy BMI 20- 25 kg/m2 and waist circumference <94 cm in men and <80 cm in women |
| Diet | Healthy well balanced diet with a low intake of saturated fat<br>Provide HEARTUK website information for heart healthy diet<br>Eating for lower cholesterol \| HEART UK - The Cholesterol Charity |
| Physical activity | Moderate intensity exercise minimum of 30 minutes- 60 minutes each day |

**Primary prevention of CVD**

- Request a full non-fasting Lipid profile for both diagnosis and monitoring patients with CVD risk.
- NICE CG181 recommends non HDL-c measured from a non-fasting blood in preference to LDL- c as the treatment goal for lipid lowering therapy. There are distinct advantages in using non-HDL cholesterol measurements (a fasting blood sample not needed, convenient for patients, cost effective. Non-HDL cholesterol includes all cholesterol present in lipoprotein particles considered to be atherogenic, (includes low-density lipoprotein (LDL), Lipoprotein (a), intermediate-density lipoprotein and very-low-density lipoprotein) and has been suggested to be a better tool for cardiovascular (CVD) risk assessment than LDL-c.
- Systemic conditions like Diabetes, Hypothyroidism, Obstructive liver disease, Nephrotic syndrome, Renal failure, Myeloma, pregnancy, medications

(corticosteroids, Androgenic steroids, contraceptive therapy, Thiazides, non-selective β-blockers, Retinoic acid derivatives, HRT, sertraline, atypical antipsychotics, antiretroviral therapy), SLE, hypopituitarism may present with dyslipidaemia.

- Do a full secondary screen for dyslipidaemia (U&E, LFT, TSH, HbA1c, urine dipstick).
- Patients with Familial Hypercholesterolaemia, markedly elevated single risk factors, in particular TC ≥ 8 mmol/L and LDL-C ≥ 4.9 mmol/L or BP ≥180/110 mmHg, Diabetes with target organ damage (nephropathy) or a duration ≥ 10 years or another additional risk factor, patients with type 1 Diabetes > 40 years of age, Chronic kidney disease stage 3 A &B (eGFR 30-59 mL/min/1.73 m2) with or without albuminuria are at high CVD risk.
- Estimate CVD risk using QRISK3 algorithm https://qrisk.org/three/ on adults aged up to 84 years of age.
- Document smoking status, diabetes status, family history of premature coronary artery disease, chronic kidney disease, therapy for hypertension, migraines, Systemic Lupus Erythematosus, regular glucocorticoid therapy, Rheumatoid arthritis, atrial fibrillation, atypical antipsychotics, erectile dysfunction, BMI and BP.
- Do not use QRISK in:
    - Patients with Familial Hypercholesterolaemia or inherited disorders of lipid metabolism
    - Patients with established CVD
    - Patients with type 1 diabetes, or eGFR less than 60 mL/min/1.73 m2 and/or albuminuria.
    - Patients aged ≥ 85 (at increased risk of CVD because of age alone particularly people who smoke or have raised BP).
- Patients with CVD risk of ≥ 10% (QRISK-3) need an informed discussion to address modifiable risk factors including smoking cessation (if applicable), moderation of ethanol intake, low saturated fat intake in the diet and moderate physical activity (30-60 minutes each day). Use CVD risk tool (above) for further information.
- If a patient is being considered for lipid lowering treatment, ensure the drug is appropriate to the individual patient, especially in elderly patients with polypharmacy, multiple co-morbidities or in women of childbearing potential.
- If lifestyle modification is inappropriate or ineffective, commence Atorvastatin 20mg once daily. Counsel the patient that statin drugs are generally safe but, very rarely, they can cause muscle damage, so if they develop severe muscle aches or muscle weakness to discontinue all lipid-lowering drugs and seek medical advice.
- Review concordance with lipid lowering therapy, dietary, lifestyle changes and repeat lipid profile, and LFT's in 3 months.

- Titrate lipid lowering therapy (Atorvastatin to 40 mg once daily ± Ezetimibe 10mg daily) to achieve Non-HDL C target of >40% reduction from baseline in all patients except for patients with Familial Hypercholesterolaemia. Assess further response after 3 months.
- For Patients with possible Familial Hypercholesterolaemia, consider referral to the Yorkshire and Humber FH service for FH genetic testing, if not done already.
- In patients with Familial Hypercholesterolaemia, LDL-C target is >50% reduction from baseline. Titrate Atorvastatin to 40 mg once daily ± Ezetimibe 10mg daily. Assess response after 3 months.
- In patients with Familial Hypercholesterolaemia, if LDL-C is ≥ 5mmol/L despite maximal tolerated lipid lowering therapy (statins ± Ezetimibe), refer to lipid clinic for consideration of PCSK9 inhibitors.
- Do not routinely measure CK activity unless the patients in symptomatic or has muscle pain before initiation of statin therapy.

**Secondary prevention of CVD**

- This category includes all patients with clinical Atherosclerosis e.g. Myocardial Infarction, Acute Coronary Syndrome, Angina, Stroke, Transient Ischaemic Attack, Peripheral Vascular Disease inclusive of revascularisation procedures, Abdominal aortic aneurysm including surgery.
- Start High intensity statins in all patients with Acute Coronary syndrome as early as possible, regardless of initial LDL-C values, unless there are any contraindications or intolerance.
- Consider addition of ezetimibe 10 mg once daily after repeat lipid profile in 2-3 months, in all patients with ACS not treated to LDL-C target of ≤ 2.0 mmol/L, despite maximal tolerated dose of statins.
- Refer to lipid clinic for PCSK9 inhibitors initiation if:
    - LDL –Cholesterol is persistently elevated ≥ 4mmol/L in patients at high risk of CVD and ≥ 3.5 mmol/L if at very high risk of CVD, despite maximal tolerated lipid lowering therapy (statins ± Ezetimibe).
    - High risk 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; chronic heart disease; ischaemic stroke; peripheral arterial disease.
    - Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (poly vascular disease).
    - Current lipid lowering therapy (statin ± Ezetimibe 10mg daily) should continue with PCSK9I therapy.

- Initiate Inclisiran if:
  - LDL-C ≥ 2.6 mmol/L (Non-HDL-C ≥ 3.5mmol/L), despite maximal tolerated lipid lowering therapy (statins ± Ezetimibe).
  - Current lipid lowering therapy (statin ± Ezetimibe 10mg daily) should continue with Inclisiran therapy
- Initiate Icosapent ethyl if:
  Fasting triglycerides ≥1.7 mmol/L and <5.6 mmo/L on maximal tolerated statin therapy and if LDL is between 1 mmol/L and <2.6 mmol/L
  - Statin therapy should continue with Icosapent ethyl.
  - Icosapent ethyl is obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to Icosapent ethyl. Icosapent ethyl should be used with caution in patients with known hypersensitivity to fish and/or shellfish. In patients with hepatic impairment, alanine aminotransferase (ALT) concentration should be monitored as clinically indicated before the start of treatment and at appropriate intervals during treatment. Icosapent ethyl was associated with an increased risk of atrial fibrillation or flutter requiring hospitalisation in a double-blind placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or flutter. Patients, particularly those with a relevant medical history, should be monitored for clinical evidence of atrial fibrillation or atrial flutter (e.g., dyspnoea, palpitations, syncope/dizziness, chest discomfort, change in blood pressure, or irregular pulse). Electrocardiographic evaluation should be performed when clinically indicated. Treatment with Icosapent ethyl has been associated with an increased incidence of bleeding. Patients taking Icosapent ethyl along with antithrombotic agents, i.e., antiplatelet agents, including aspirin, clopidogrel and/or anticoagulants, may be at increased risk of bleeding and should be monitored periodically.

**Statin intolerance**

- In patients with intolerance or side effects to Atorvastatin therapy, see AAC Statin Intolerance Algorithm for advice regarding adverse effects. https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-Intolerance-Pathway-NEW.pdf
- Consider Ezetimibe 10mg daily monotherapy (or in addition to maximal tolerated dose of statins). Assess response after 3 months.
- Initiate Bempedoic acid 180 mg daily in combination with Ezetimibe 10 mg daily when ezetimibe monotherapy does not achieve treatment targets. Assess response after 3 months.

- In patients with Familial Hypercholesterolaemia for primary prevention of CVD, with statin intolerance, if LDL-C ≥ 5mmol/L, despite maximal tolerated lipid lowering therapy (statins ± Ezetimibe), consider referral to lipid clinic for PCSK9 inhibitors initiation.
- For secondary CVD prevention with statin intolerance, refer to lipid clinic for PCSK9 inhibitors initiation if, LDL-C ≥ 2.6 mmol/L (Non-HDL-C ≥ 3.5mmol/L) despite maximal tolerated lipid lowering therapy (statins ± Ezetimibe).

**Monitoring on lipid lowering therapy**

| Time | Investigations |
|---|---|
| Baseline | Full lipid profile, U&E, LFT, TSH, HbA1c, urine dipstick |
| 3 months post statin initiation | Full lipid profile, LFT |
| 6-9 months, statin Rx up titration or addition of Ezetimibe | Full lipid profile, LFT |
| 12 months and then annually | Full lipid profile, LFT |

**CVD Lipid lowering treatment targets**

| | | |
|---|---|---|
| Primary prevention of CVD | Familial Hypercholesterolaemia | LDL-C target >50% reduction from baseline |
| | Primary Non FH or mixed hyperlipidaemia | Non-HDL-C target >40% reduction from baseline |
| Secondary prevention of CVD | | LDL-C target of ≤ 1.8 mmol/L or Non-HDL-C target of ≤ 2.5 mmol/L |

**Special considerations with lipid lowering therapy**

- A fully informed discussion is indicated in female patients in the reproductive age group prior to initiation of lipid lowering therapy inclusive of contraindications to lipid lowering therapy (Statins, ezetimibe, PCSK9I, Fibrates), need for screening children for Familial Hypercholesterolaemia (Autosomal dominant inheritance with 50% risk of inheritance) and risks to the foetus if lipid lowering therapy is continued.
- Patient who conceive on lipid lowering therapy should stop therapy immediately and be offered *urgent referral* for foetal assessment.
- In female patients with heterozygous Familial Hypercholesterolaemia, there is no indication to monitor lipid profile during pregnancy and breast feeding period.

- Annual review needs to take into account all CVD risk factors, treatment to target LDL-C/Non-HDL-C, concordance with lipid lowering therapy, diet and lifestyle. If applicable, a discussion on screening immediate family and conception plans is needed.
- For lipid lowering therapy initiation (or changes) in patients with chronic kidney disease with eGFR< 30mL/min, consider referral to lipid clinic.

| Red drugs | Amber 1 drugs | Green drugs |
|---|---|---|
| PCSK9 Inhibitors<br>- Evolocumab<br>- Alirocumab | Inclisiran<br>Icosapent ethyl<br>Bempedoic acid or Ezetimibe and Bempedoic acid combination treatment | Statins<br>Ezetimibe<br>Fibrates |

**Familial Hypercholesterolaemia**

Familial Hypercholesterolaemia (FH) is an Autosomal dominant condition resulting in high LDL-cholesterol levels from birth with premature coronary heart disease (CHD) occurring in approximately half of men by age 50 and one third of women by age 60. Lifetime exposure to LDL-C correlates with increased risk of cardiovascular disease. The prevalence of heterozygous FH is 1 in 250. Early initiation of lipid lowering treatment combined with lifestyle modification can virtually eliminate any additional risk and potentially restore life expectancy to normal. The Yorkshire and Humber Familial Hypercholesterolaemia service identifies individuals with FH through genetic testing and offers cascade testing to family members where a pathogenic mutation has been identified. The Yorkshire and Humber Familial Hypercholesterolaemia service is based at 4 different Trusts including Huddersfield, Hull, Leeds and York and has a standardised FH genetic testing pathway for adults with FH with agreed local arrangements for the provision of Paediatric FH service. Refer to the primary care pathway for identification of patients with FH and primary and secondary CVD prevention pathway in the CVD risk optimisation tool kit for clinical management of FH. The FH service based at Hull University Teaching Hospitals NHS Trust offers extended service to the primary care networks in Hull, East Riding of Yorkshire, North Lincolnshire and North East Lincolnshire.

Yorkshire and Humber FH Service contacts:

| Site | Contact |
|---|---|
| Calderdale & Huddersfield NHS Foundation Trust | Ms Jillian Webster, FH nurse specialist<br>Dr Karen Mitchell, Consultant Chemical Pathology |
| Hull University Teaching Hospitals NHS Trust | Ms Paula Sutton - FH nurse specialists<br>Ms Rachel Dunn- FH nurse specialist<br>Dr Deepa Narayanan- Consultant in Chemical Pathology & Metabolic Medicine<br>Dr Robert Desborough- Consultant in Chemical Pathology & Metabolic Medicine |
| Leeds Teaching NHS Hospitals Trust | Ms Claire Burton, FH nurse specialist<br>Dr Michael Mansfield, Consultant in diabetes and lipidology<br>Dr Kevin Stuart, Consultant Chemical Pathology & Metabolic Medicine |
| York Teaching Hospitals NHS Foundation Trust | Ms. Claire Tuson, FH nurse specialist<br>Dr Deepak Chandrajay, Consultant Chemical Pathology & Metabolic Medicine |

**Paediatric Familial Hypercholesterolaemia pathway**

Paediatric FH pathway.pdf

**Hypertriglyceridaemia Pathway**

Hypertriglyceridaemia pathway.docx.pdf

**Referral criteria to lipid clinic to HUTH**

- Initiation of PCSK9 Inhibitors
- Not treated to LDLC targets despite maximal lipid lowering therapy
- Intolerance to 3 different statins
- Statin contraindication
- LFT abnormalities on statins
- Rhabdomyolysis on statins
- Possible Familial Hypercholesterolaemia

- Patients with triglyceride concentration ≥ 20 mmol/L or sustained triglyceride ≥10 mmol/L in the absence of known secondary causes of dyslipidaemia and history of pancreatitis

**Electronic referral service**

Choose and book service- For lipid clinic/ FH service referrals, via ERS, select lipid/ Familial Hypercholesterolaemia service under Endocrinology and refer to DOS for Chemical Pathology service.
Advice and guidance- For advice and guidance queries regarding lipids or Familial Hypercholesterolaemia, via ERS, select lipid service under Endocrinology.

**References**


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10. https://www.sunderlandccg.nhs.uk/wp-content/uploads/2021/07/Northern-England-Evaluation-and-Lipid-Intensification-Guideline-NEELI.pdf
11. https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/Lipid-Management-Pathway-NEW-version-4.pdf

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Appendix

Appendix A

## Referral pathway for adult patients with suspected Familial Hypercholesterolemia (FH)

# This page is currently being updated and will be replaced when update complete.

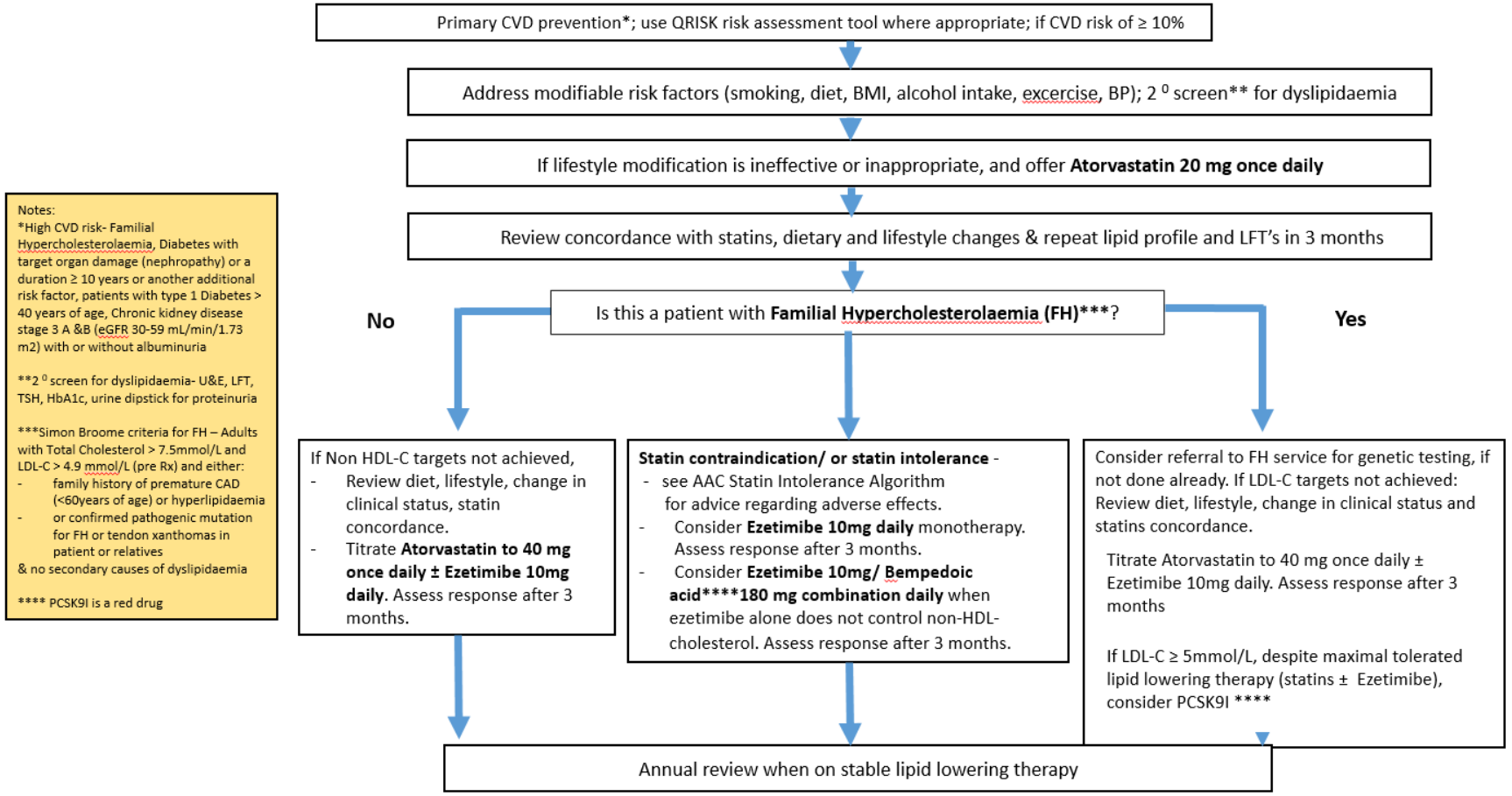
# Most recent available version -

PowerPoint Presentation (valeofyorkccg.nhs.uk)

Appendix B: Primary CVD Prevention Pathway

NHS Hull University Teaching Hospitals NHS Trust

# Primary prevention of CVD lipid lowering pathway




Notes:
*High CVD risk- Familial Hypercholesterolaemia, Diabetes with target organ damage (nephropathy) or a duration ≥ 10 years or another additional risk factor, patients with type 1 Diabetes > 40 years of age, Chronic kidney disease stage 3 A &B (eGFR 30-59 mL/min/1.73 m2) with or without albuminuria

**2 0 screen for dyslipidaemia- U&E, LFT, TSH, HbA1c, urine dipstick for proteinuria

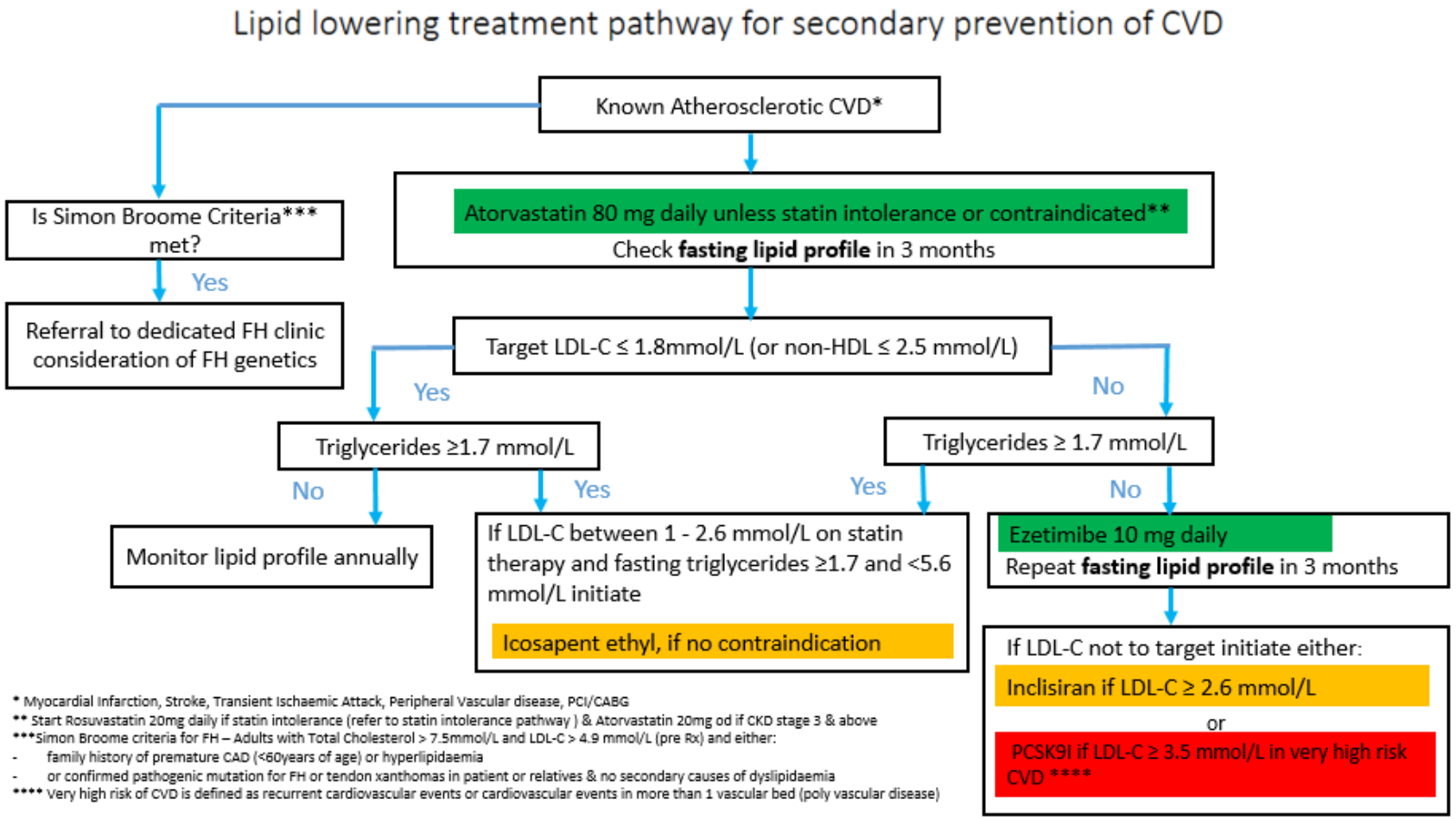
***Simon Broome criteria for FH – Adults with Total Cholesterol > 7.5mmol/L and LDL-C > 4.9 mmol/L (pre Rx) and either:
- family history of premature CAD (<60years of age) or hyperlipidaemia
- or confirmed pathogenic mutation for FH or tendon xanthomas in patient or relatives

& no secondary causes of dyslipidaemia

**** PCSK9I is a red drug

BETTER BRIGHTER GREENER FAIRER

Appendix C: Secondary CVD Prevention Pathway



# Appendix D: Statin Intolerance Pathway

## Introduction

- Statins are the cornerstone for prevention and treatment of cardiovascular (CV) disease with a substantial evidence of reduction of morbidity and mortality. Refer to Lipid Management Pathway and related NICE guidelines (CG181, CG71) for guidance on initiation, titration and monitoring of statin therapy.
- In clinical trials, statins were found to be largely well tolerated (often with a similar adverse effect (AE) profile to placebo), however this is not reflected in clinical practice where up to 75% of people started on a statin will discontinue treatment within 2 years.
- Stopping statin therapy is associated with an increased risk of major CV events and there is growing concern that clinicians are labelling patients as **'statin intolerant'** too quickly. Indeed statin discontinuation is significantly associated with negative media coverage.

### Definition of Statin Intolerance

- Intolerance to initial statin therapy is defined by NICE as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- Other definition: 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)

- 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) consider other musculoskeletal disorders, metabolic, degenerative or inflammatory e.g. Vitamin D deficiency, polymyalgia rheumatica. Check Bone profile, Vit D, CRP.

## Considerations when starting a statin to reduce risk of SRM

- Check baseline thyroid, liver and renal function, any potential drug interactions, and avoid the highest doses in at risk groups (See "Risk Factors" below).
- Ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure CK. If CK levels are > 4x ULN do not start statin - investigation required.
  ***Do not measure CK if person is asymptomatic.***
- Warn patients about AEs, specifically muscle symptoms. Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure CK (see page 1).

## Risk factors for SRM and statin intolerance

***Endogenous factors***

- Female gender
- Advanced age (> 75 yrs)
- Frailty (reduced lean body mass)
- History of muscle disorder or high CK
- Impaired renal or hepatic function
- Personal or family history of intolerance to lipid-lowering therapies.
- Hypothyroidism

***Exogenous Factors***

- Excessive alcohol intake
- High intensity exercise
- Dehydration
- Drug interactions with statins (including herbal medicines)
- Vitamin D deficiency

## Classification of statin related muscle toxicity (SRM)

*Alfirevic A. et. al. Clin Pharm Ther. 2014; 96:470–476*

| SRM | Phenotype | Incidence | Definition |
|---|---|---|---|
| SRM 0 | CK elevation <4x ULN | 1.5-26% | No muscle symptoms |
| SRM 1 | Myalgia, tolerable | 190/100,000 Patient-years; 0.3-33% | Muscle symptoms without CK elevation |
| SRM 2 | Myalgia, intolerable | 0.2-2/1,000 | Muscle symptoms, CK <4x ULN, complete resolution on dechallenge |
| SRM 3 | Myopathy | 5/100,000 Patient-years | CK elevation >4x ULN <10x ULN ± muscle symptoms, complete resolution on dechallenge |
| SRM 4 | Severe myopathy | 0.11% | CK elevation >10x ULN <50x ULN, muscle symptoms, complete resolution on dechallenge |
| SRM 5 | Rhabdomyolysis | 0.1-8.4/100,000 | CK elevation >10x ULN with evidence of renal impairment + muscle symptoms or CK >50x ULN |
| SRM 6 | Autoimmune-mediated necrotizing myositis (SINAM) | ~2/million per year | Detection of HMGCR antibodies, HMGCR expression in muscle biopsy showing autoimmune myositis, incomplete resolution on dechallenge |

HMGCR = 3-hydroxy-3-methylglutaryl coenzyme A reductase ULN = upper limit of normal

- SRM is a spectrum from myalgia to severe myopathy
- SRM 0 - does not preclude statin therapy, consider reducing starting dose
- SRM 1-3 manage according to pathway
- When SRM4 is suspected, without evidence of impaired renal function, discontinue statin therapy immediately and refer for outpatient assessment. Assess and treat possible contributory factors and re-assess the need for a statin. Intensify lifestyle modifications and consider alternative lipid lowering regimens.
- If rhabdomyolysis (SRM5) is suspected, immediately stop statins, urgently refer to inpatient assessment and management including intravenous rehydration as required to preserve renal function. Do not wait for measurement of urinary myoglobin. Post recovery, manage as for SRM4.
- Statin induced necrotizing autoimmune myositis (SINAM) (SRM6) should be suspected in patients with progressive muscle weakness and ongoing CK elevation despite statin withdrawal. Requires immunosuppressive treatment and avoidance of re-exposure to statins. Re-assess the need for lipid lowering therapy - may be eligible for treatment with PCSK9 inhibitor (NICE TA 393, 394).

## Person-centred approach to address statin intolerance

### Initial Consultation

- Be aware of "nocebo effect"[1] and "statin reluctance"[2]
- Reinforce healthy lifestyle habits (e.g. exercise, reducing weight)
- Listen to the concerns of each patient.
- Explain LDL-C targets and strategies to lower LDL-C/non-HDL-C
- Discuss options to reduce LDL-C/ non-HDL-C with pros and cons
- Explain the benefits of statins
- Evaluate and identify any risk factors and address (e.g. drug interactions)
- Work with patients to identify and agree best options and next steps

### Follow up

- Follow up on agreed plan and address any issues/concern.
- Advise patients to contact you if they experience muscle symptoms
- Ongoing patient education and reg review helps addressing concerns around medicine safety and underl the importance of adherence.

(1) **Nocebo effect** is negative expectations o the patient regarding a treatment leading t reporting more negative effects even if the are prescribed a placebo.

(2) **Statin reluctance** is an attitudinal state of aversion to taking statins (often without pr exposure).

## Statin-based approaches to manage muscle symptoms

- Adopt person-centred approach as described above.
- Therapy with a lower dose statin is preferred to no statin
- Apply a repetitive "De-Challenge" - "Re-Challenge" approach to establish if symptoms are caused by a statin(s) and the best statin regimen for each patie
- Switch to a different statin or re-challenge with the same statin using a lower d or frequency (intermittent dosages)
- Patients who do not tolerate statins on a daily basis, alternate day or twice-wee dosing is a good option.
- Rosuvastatin and atorvastatin have longer half-lives, permitting their use on a non-daily regime.
- Adding ezetimibe to a lower dose statin may be better tolerated with robust reduction of LDL-C / non-HDL-C .
- Once a new regime is tolerated, dose / frequency can be up-titrated slowly to achieve LDL-C / non-HDL-C goals with minimal or no muscle complaints.

*It is important to note that cardiovascular benefits have not been proven for all t above approaches but any reduction of LDL-C / non-HDL-C is beneficial.*

## LDL-C lowering options for patients with genuine statin intoleranc

- Refer to the AAC Lipid Management Algorithm. (click here)
- Consider ezetimibe, (NICE TA 385) therapy as per algorithm
- Consider ezetimibe combined with bempedoic acid (NICE TA 694) as per algorit
- Consider PCSK9i if eligible for treatment according to NICE TA 393, 394

## Non-muscle related statin side effects

May vary between different statins. In clinical trials some side effects often associated with statins are not statistically different from placebo.

***Most commonly reported:*** gastrointestinal disturbance and asymptomatic increases in hepatic transaminases (ALT or AST). May affect up to 1 in 10 statin users.

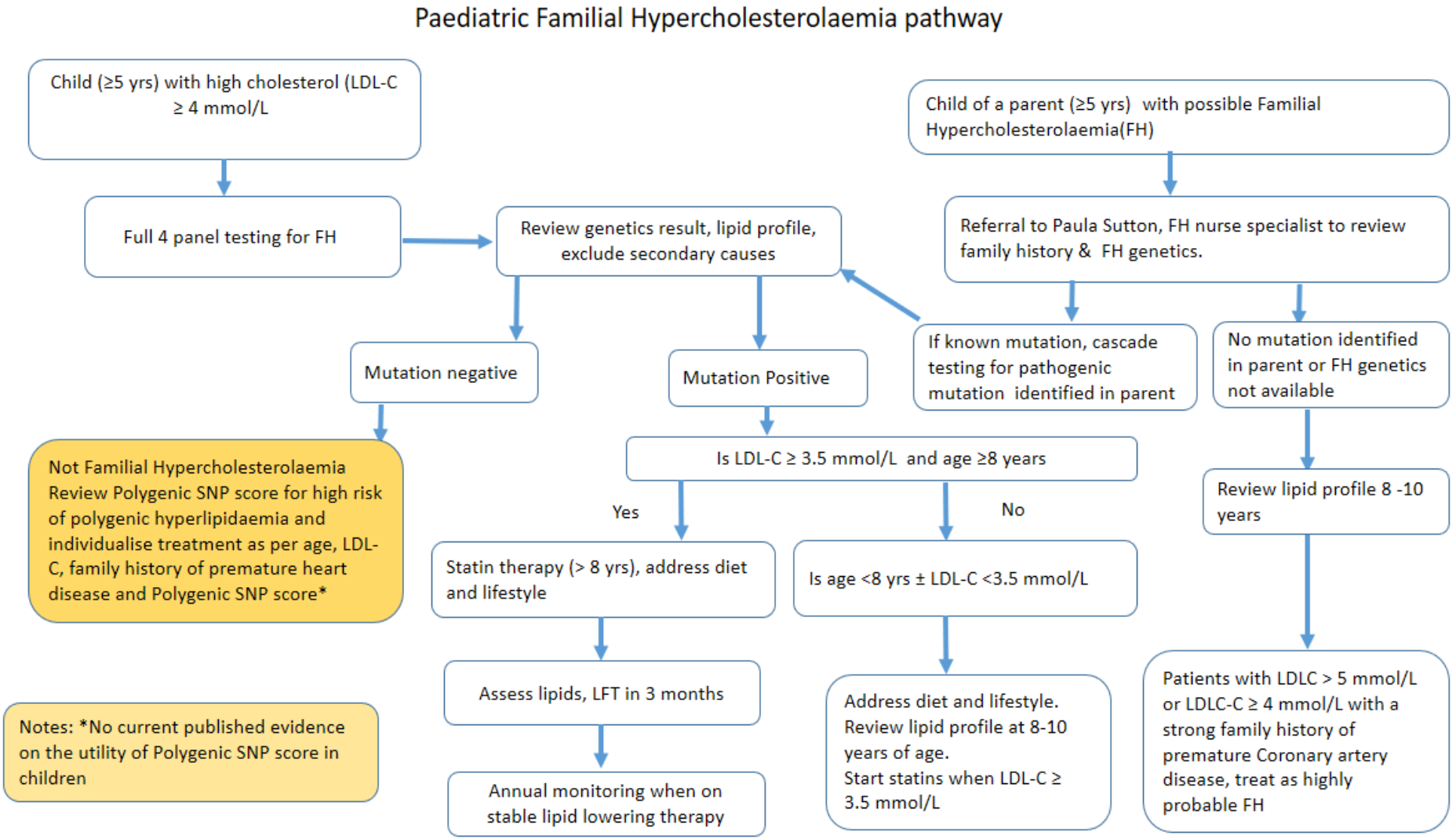
***Rarer side effects include:*** Hepatotoxicity, new onset Type 2 Diabetes (benefits outweigh risk, do not stop statin), Renal insufficiency, proteinuria, Neurocognitive and neurological impairments (no apparent link from RCTs), Intracranial haemorrhage (conflicting evidence, benefit outweigh possible harm), Interstitial lung disease, Pancreatitis, Skin disorders including alopecia, Lupus-like reaction, Sleep disturbance, headache, dizziness, fatigue, depression, sexual dysfunction.

***Management:*** If symptoms appear statin related, consider de-challenge and re-challenge or change to a different statin (e.g. hydrophilic instead of lipophilic).

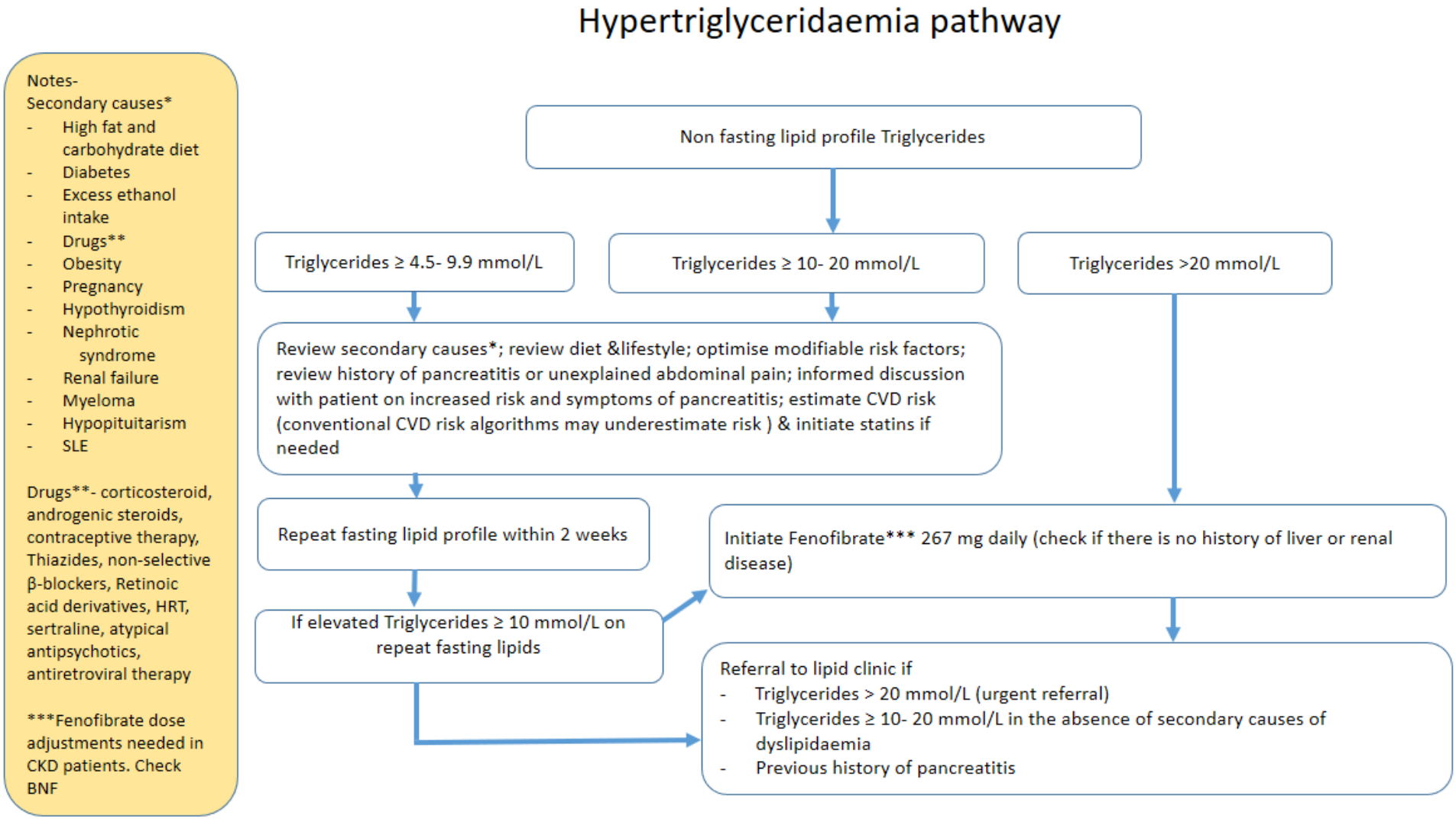
Liver enzyme abnormalities - minor increases in liver enzymes (<2x ULN) may be seen within the first three months of statin therapy; temporary discontinuation and furthe assessment is warranted if levels exceed 3x ULN. Several studies have confirmed that the cardiovascular benefits of statin treatment in high-risk populations outweigh the rare adverse effects, such as rhabdomyolysis.

**Authors:** Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. June 2021. Review date: June 2022.
Pathway approved by NICE July 2021. Please refer to the Lipid Management Pathway and Full List of References (click here).

Appendix E: Paediatric FH Pathway



Appendix F: Hypertriglyceridaemia Pathway



## Appendix G – Procedural Document Checklist for Ratification

The below document is to be completed following the development or amendment of any procedural document prior to ratification of the document:

| | |
|---|---|
| **Document title:** | CVD Risk Optimisation and Lipid Lowering Therapy Guidelines |
| **Type of procedural document:**<br>*(delete as appropriate)* | Guideline |
| **Name of document author:** | Dr D Narayanan |
| **Name of committee for document ratification:** | Clinical Support Health Group |

| **Checklist for the Review and Approval of Procedural Documents** | **Yes/No/ Unsure** |
|---|---|
| **Title** | |
| Is the title clear and unambiguous? | Yes |
| Is it clear whether the document is a policy, procedure, guideline or standard operating procedure? | Yes |
| **Document Control** | |
| Is the correct version number recorded on the policy? | Yes |
| Is the document control box fully completed and accurate? | Yes |
| Are keywords available to enable searches for the document on the Trusts intranet site? | Yes |

| Checklist for the Review and Approval of Procedural Documents | Yes/No/ Unsure |
|---|---|
| **Contents** | |
| Is there a contents page available? | Yes |
| Can the contents page take you to various sections within the document? | Yes |
| **Summary** | |
| Does the information summarise the content of the procedural document clearly, enabling the reader to be confident that the correct document has been accessed? | Yes |
| **Purpose** | |
| Does this section outline the objectives and intended outcomes of the process/system being described? Is there a clear purpose stated for the procedural document? | Yes |
| **Responsibilities, Accountabilities and Duties** | |
| Does this section provide an overview of the individual, departmental and committee duties including levels of responsibility for document development? | Yes |
| **Procedural documentation details** | |
| Does this provide details of the procedural documentation? | Yes |
| If lengthy, is it presented in clearly defined subsections to make it easier for the reader to refer to? | Yes |
| **Process for Monitoring Compliance** | |
| Are there measurable standards to support monitoring compliance of the document? | Yes |
| Is there a plan to review or audit compliance with the document? | Yes |

| Checklist for the Review and Approval of Procedural Documents | Yes/No/ Unsure |
|---|---|
| Has any plan to use clinical audit been discussed with the Clinical Audit Department and included in the Trust Clinical Audit Programme? | Yes |
| **Equality Impact Assessment (EIA)** | |
| Has an EIA been completed as part of the document development/review process? | Yes |
| Has the EIA been approved by the Trust Equality and Diversity Lead? | Yes |
| Has any privacy, dignity and respect issues been identified within the procedural document? If so does the document indicate how these will be addressed? | Yes |
| **Referencing** | |
| Is the type of evidence to support the document identified explicitly? | Yes |
| Are key references cited? | Yes |
| Are the references cited in full using the Harvard referencing style and in alphabetical order? *The following are examples of how to cite references using the Harvard Style*<br>• **Books:** Surname, Initial. (Year of publication) Title. Edition if later than first. Place of publication: publisher. Series and volume number if relevant.<br>• **Journal articles:** Surname, Initial. (Year of publication) 'Title of article', Title of Journal, volume number (issue number), page reference. doi: doi number if available OR Available at: URL (Accessed date).<br>• **Web Pages:** Surname, Initial or Organisation (Year that the site was published/last updated) Title of web page. Available at: URL (Accessed: date). | |

| Checklist for the Review and Approval of Procedural Documents | Yes/No/ Unsure |
|---|---|
| *Further information can be found at: Open University (2022) Quick guide to Harvard referencing available at: https://www.open.ac.uk/library/referencing-and-plagiarism/quick-guide-to-harvard-referencing-cite-them-right (Accessed 12/1/2022)* | |
| Are the links referenced in the procedural document working and take you direct to the source material? | Yes |
| Are local/organisational supporting documents referenced? | Yes |
| **Development Process** | |
| Was the document reviewed before the agreed review date expired? | Yes |
| If not please state reason for delay? | NA |
| Do you feel a reasonable attempt has been made to ensure relevant expertise has been used? | Yes |
| Is there evidence of consultation with relevant stakeholders and users detailed in the tracking document? | Yes |
| Have the following been considered as part of the development of this document:<br>• Mental Capacity Act<br>• Privacy, Dignity and Respect<br>• Safeguarding<br>• Fraud<br>• Infection Control<br>• Training requirements<br>• Other relevant documents | Yes |
| **Formatting** | |

| **Checklist for the Review and Approval of Procedural Documents** | **Yes/No/ Unsure** |
|---|---|
| Is the same font and size used throughout the document? (Arial 11) | Yes |
| Is the line spacing set at multiple, 1.15? | Yes |
| Are the headings and sub headings displayed using the following shape bullet point?<br>• **1 Heading**<br>• **1.1 Sub Heading**<br>• ***1.1.1 Sub heading*** | Yes |
| Is the text set at left-hand margin? | Yes |
| Has the page number been included? | Yes |
| Does the procedural document refer to a person's job title rather than personal names wherever possible? | Yes |
| Are the margins set at 'Moderate'? | Yes |