Mid and South Essex Integrated Care System

Adult Lipid Management for Primary and Secondary Prevention of Cardiovascular Disease (CVD)

NHS

• Measure non-fasting ***full lipid profile*** (total cholesterol, HDL-C, non-HDL-C, triglycerides) and HbA1c as part of an initial baseline assessment. • Consider secondary causes of hyperlipidaemia and manage as needed. • Ensure appropriate baseline and follow up tests as detailed on page 2. Measure BMI, BP, assess alcohol consumption and smoking status. • If non-fasting triglyceride above 4.5mmol/L see page 2.

PRIMARY PREVENTION

Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate (see page 2, *'Primary Prevention Risk Assessment'*).

- Age ≤84 & QRISK ≥10% over next 10 years
- Type 2 diabetes & QRISK ≥10% over next 10 years
- Type 1 diabetes, if they have one or more of the following:
  - Over 40 years
  - Had diabetes for >10 years
  - Have established nephropathy
  - Have other CVD risk factors
- CKD eGFR < 60 mL/min/1.73m² and/or albuminuria
- Age ≥85 years if appropriate consider comorbidities, frailty & life expectancy

Identify and optimise the management of all modifiable CVD risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c (re-calculate CVD risk using QRISK if indicated). Treat secondary causes of high cholesterol (such as hypothyroidism, liver disease and nephrotic syndrome). Discuss the risk of CVD and benefits and risks of statin treatment with patient.

Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors).

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate offer high intensity statin unless CI.

Atorvastatin 20mg OD GREEN TLS

- Measure full lipid profile after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months:
  - Discuss treatment adherence, timing of dose, diet and lifestyle measures.
  - If at higher CVD risk (based on comorbidities, risk score or clinical judgement - see page 2 *'Additional Risk Factors'*) consider increasing the dose of atorvastatin every 2 to 3 months up to a maximum dose of atorvastatin 80mg daily. For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- Measure lipid profile at least 3 months after each dose adjustment or medication change.

- If patients on a high-intensity statin have adverse effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*).
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value after appropriate dose titrations consider adding **ezetimibe 10mg** daily GREEN TLS (NICE TA385).
- If statin treatment is contraindicated or not tolerated:
  - Follow *Statin Intolerance Algorithm* for advice regarding adverse effects (click here).
  - **Ezetimibe 10mg** GREEN TLS monotherapy may be considered (NICE TA385). Assess response after 3 months.
  - **Ezetimibe 10mg/bempedoic acid 180 mg** GREEN TLS combination may be considered when ezetimibe alone does not control non-HDL-C/LDL-C well enough (NICE TA694).

If non-HDL-C reduction remains < 40% of baseline value despite maximum tolerated lipid lowering therapy (including people with intolerances and contraindications) consider referral to specialist lipid management clinic.

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, and/or a personal and/or family history of confirmed CHD (<60 years) and with no secondary causes: suspect familial hypercholesterolaemia (FH) (possible heterozygous FH).
Do not use QRISK risk assessment tool

DIAGNOSIS AND REFERRAL

Take fasting blood for repeat lipid profile to measure LDL-C.
Use the **Simon Broome** or **Dutch Lipid Clinic Network** (DLCN) criteria to make a **clinical diagnosis of FH**.

Refer to lipid clinic for further assessment if **clinical diagnosis of FH** or if TC>9.0mmol/L and/or LDL-C >6.5mmol/L and/or non-HDL-C >7.5mmol/L or fasting triglycerides > 10mmol/L (regardless of family history) (page 2)

TREATMENT TARGETS IN FH

If clinical diagnosis of FH follow the recommended treatment management pathway for primary or secondary prevention as for non-FH, ***BUT***
aim to achieve at least a 50% reduction of LDL-C (or non-fasting non-HDL-C) from baseline.
Consider specialist referral for further treatment and or consideration of injectable therapies* such as PCSK9i therapy RED TLS **if:**

- they are assessed to be at very high risk of a coronary event**
- OR therapy is not tolerated/contra-indicated
- OR LDL-C remains >5mmol/L (primary prevention)
- OR LDL-C remains >3.5mmol/L (secondary prevention)

despite maximum tolerated or licensed statin dose and ezetimibe therapy.

**defined as any of the following:
- Established coronary heart disease
- A family history of premature CHD (NICE).
- Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes acute coronary syndromes (ACS), angina, previous myocardial infarction (MI), revascularisation, stroke or transient ischaemic attack (TIA), symptomatic peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA). Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours).
Identify and optimise the management of all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c. Treat secondary causes of high cholesterol (such as hypothyroidism, liver disease and nephrotic syndrome). Discuss the risk of CVD and benefits and risks of statin treatment with patient.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors.
Offer a high intensity statin unless contraindicated.
Atorvastatin 80mg OD GREEN TLS
Use a lower dose of atorvastatin if there is a potential drug interaction, high risk of or experiencing adverse effects, or patient preference.
Offer atorvastatin 20mg if CKD (people with eGFR< 60 mL/min/1.73m²).

- Measure full lipid profile after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months:
  - Discuss treatment adherence, timing of dose, diet and lifestyle measures.
  - Consider increasing the dose of atorvastatin if started on less than 80 mg a day if the person is judged to be at higher CVD risk because of comorbidities, risk score, or using clinical judgement - see page 2 *'Additional Risk Factors'*. For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- If non-HDL-C baseline value is not available*, consider target non-HDL-C < 2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/L) as recommended by Joint British Societies (JBS3).
  **this scenario is not covered by NICE CG181*
- If patients on a high-intensity statin have adverse effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*).

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

If statin treatment is contraindicated or intolerance confirmed, consider:
- **Ezetimibe 10mg** GREEN TLS monotherapy (NICE TA385). Assess response after 3 months.
- **Ezetimibe 10mg/bempedoic acid 180 mg** GREEN TLS combination when ezetimibe alone does not control non-HDL-C sufficiently (NICE TA694).

If non HDL-C remains > 2.5mmol/L consider injectable therapies* - arrange a fasting blood test to measure LDL-C and assess eligibility criteria (NICE TA393/394, NICE TA733).

If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 3 months confirm statin adherence, then consider the following options based on shared decision making (see page 2) with the patient.

Add ezetimibe 10mg GREEN TLS (NICE TA385).
Reassess after 3 months.

If non HDL-C remains > 2.5mmol/L consider injectable therapies* - arrange a fasting blood test to measure LDL-C and assess eligibility criteria (NICE TA393/394, NICE TA733).

Injectable therapies*

If non-HDL-C > 2.5mmol/L - arrange a fasting blood test to measure LDL-C and assess eligibility criteria:

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

OR

- **PCSK9i** RED TLS - see overleaf for LDL-C thresholds (NICE TA393/394)

If eligibility criteria are not met, consider **ezetimibe 10mg** GREEN TLS (if not previously considered)
*Inclisiran and PCSK9i should not be prescribed concurrently

MANAGEMENT

This guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. 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 (in accordance with NICE TA eligibility criteria). 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 m^2 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 people:

- severe obesity (BMI > 40kg/m^2) 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/1.73m^2 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/1.73m^2 or more.

Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m^2

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**
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

- **All statins have been assigned a GREEN TLS.**
- **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 GREEN TLS** 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: alirocumab and evolocumab RED TLS** (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 GREEN TLS** when combined with ezetimibe (NICE TA694) produces an additional LDL-C reduction of approximately 28% (range 22-33%) but no clinical outcome evidence is currently available.
- **Inclisiran RED TLS** (NICE 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 persistent 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	✓	✓	✓	✓
Annually	✓*		✓*	

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, adverse effects, 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	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)
Secondary Prevention		
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 Joint British Societies' JBS3 consensus recommendation.
Non-HDL-C = TC minus HDL-C
LDL-C = non-HDL-C minus (Fasting triglycerides[a]/2.2)
[a] valid only when fasting triglycerides are less than 4.5 mmol/L

SPECIALIST SERVICES

Scope of specialist service available locally may include: lipid clinic, PCSK9i clinic (offering initiation and subsequent follow up), FH genetic diagnosis and cascade testing, lipoprotein apheresis service. NICE eligibility criteria for PCSK9i therapy 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).

TRIGLYCERIDES

Triglyceride concentration	Action
	Review for potential secondary causes of high triglycerides
Greater than 20mmol/L	**Refer to lipid clinic for urgent specialist review** if not a result of excess alcohol or poor glycaemic control. Unless contraindicated offer high intensity **statin** or **fenofibrate** (if not already on statin) **GREEN TLS** whilst awaiting advice. 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. Unless contraindicated offer high intensity **statin** or **fenofibrate** (if not already on statin) **GREEN TLS** whilst awaiting advice. Seek specialist advice if the TG concentration remains > 10mmol/L. 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/L.

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 *Statin Intolerance Algorithm* (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
Acknowledgements	Dr Rani Khatib & Dr Dermot Neely, Accelerated Access Collaborative
Version	2.0
Author	Accelerated Access Collaborative; adopted for local use by Dr Iyer and MSEMOC working group
Approved by	MSEMOC
Date Approved	December 2022
Review Date	December 2027 or earlier subject to any new updates nationally