HNY ICB Guidance for Lipid Management for Primary and Secondary Prevention of CVD

INITIAL CONSIDERATIONS:

● 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. ● Identify and exclude people with contraindications/drug interactions ● If non-fasting triglyceride above 4.5mmol/L see page 2.

PRIMARY PREVENTION

Offer lifestyle changes and 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/1.73m^2 and/or albuminuria
- Age ≥85 years if appropriate consider co-morbidities, frailty & life expectancy

Discuss the benefits of lifestyle changes and identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

Offer people the opportunity to have their risk of CVD assessed again after they have tried to change their lifestyle (where applicable)

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, discuss the risks and benefits of statins, and offer treatment based on an informed shared decision.

Atorvastatin 20mg daily

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

- If patients on a high-intensity statin have side 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 2-3 months consider adding Ezetimibe 10mg daily (NICE TA385)
- If statin treatment is contraindicated or not tolerated;
  - See AAC Statin Intolerance Algorithm for advice regarding adverse effects (click here)
  - Ezetimibe 10mg monotherapy may be considered. Assess response after 2-3 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).

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

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, a personal and/or family history of confirmed CHD (<60 years) and with no secondary causes: suspect familial hypercholesterolaemia (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**.

Use clinical findings, a full lipid profile and family history to judge the likelihood of a familial lipid disorder, rather than using strict lipid cut-off values alone.

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 and/or other risk factors present 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 PCSK9i therapy IF

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

despite maximal tolerated statin and ezetimibe therapy.

**defined as any of the following:
- Established coronary heart disease
- Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes CHD, angina, Acute Coronary Syndrome (MI or unstable angina), revascularisation, stroke or TIA, or symptomatic peripheral arterial disease. Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours).

Identify and address all modifiable risk factors - smoking, diet, obesity, alcohol intake, physical activity, blood pressure and HbA1c.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors. Prescribe a high intensity statin:
Atorvastatin 80mg daily

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 GFR< 60 mL/min/1.73m^2).

- Measure full lipid profile again after 2-3 months (non-fasting).
- Aim for an LDL-C of ≤ 2.0 mmol/L, or non-HDL-C of ≤ 2.6 mmol/L
- LDL and non-HDL-C levels should be reduced as much as possible. Personalise targets based on clinical judgement and an informed discussion with patient. ***See Titration Thresholds / Targets*** **(page 2)**

- If high intensity statin treatment does not achieve expected reduction (see table on page 2) after 2 to 3 months
  - Discuss treatment adherence, timing of dose, diet and lifestyle measures
  - If started on less than atorvastatin 80mg and the person is judged to be at higher risk (based on co-morbidities or clinical judgment), consider increasing to 80mg atorvastatin or maximally tolerated dose. For how to increase in people with CKD see *'Special Patient Populations'* (page 2).
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 *'Extent of lipid lowering with available therapies'*)

Escalating lipid lowering treatment

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

- Ensure an informed discussion between the clinician and the person about the risks and benefits of additional lipid-lowering treatments.
- Take into account the person's preferences, the presence of any comorbidities, whether they are on multiple medications, whether they have frailty and their life expectancy.
- Do not routinely de-escalate lipid lowering therapies when levels are lower than NICE target, except if clinically indicated or based on the person's needs or preferences

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

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

If non HDL-C remains > 2.6mmol/L despite other lipid lowering therapies consider Injectable therapies - arrange a fasting blood test and assess eligibility criteria (TA393/394, TA733)

Ezetimibe 10mg daily (NICE TA385). Reassess after three months. If non-HDL-C remains > 2.6mmol/L; consider **injectable therapies** arrange a fasting blood test and assess eligibility

** Inclisiran and PCSK9i should not be prescribed concurrently

Injectable therapies**

If non-HDL-C > 2.6mmol/L; Arrange fasting blood test to measure LDL-C to assess eligibility:

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

OR

- **PCSK9i** - see overleaf for LDL-C thresholds. (TA393/4)

If eligibility criteria not met, consider **ezetimibe 10mg daily** (if not previously considered)

Additional CV risk reduction considerations - check fasting triglycerides levels and consider icosapent ethyl. See triglycerides section overleaf.

Consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce CVD risk further, even if the lipid target for secondary prevention of CVD is met. (NG238)

MANAGEMENT

This guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. If 40% reduction of non-HDL-C, or target levels are not achieved, offer high intensity statins. Discuss with people who are stable on a low- or medium-intensity statin the likely benefits and potential risk of side effects if changed to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.

Ezetimibe, alirocumab, evolocumab or inclisiran can be added when patients' LDL-C levels are not lowered enough with the maximally tolerated dose of statins. If statins are contraindicated or not tolerated and ezetimibe alone does not control LDL-C well enough, bempedoic acid with ezetimibe is an option. 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 NG238 and TA805 for exceptions).

PRIMARY PREVENTION RISK ASSESSMENT

Use **QRISK3** version of the calculator (or QRISK2 if not available).

- Do not use this risk assessment tool for people with established CVD or those who are already 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 < 60 mL/min/1.73 m^2 and/or albuminuria (as already at high risk of developing CVD).
- Consider people aged ≥ 85 at increased risk of CVD because of age alone particularly people who smoke or have raised BP.
- If QRISK <10% over next 10 years, do not rule out treatment if there is an informed preference for taking a statin or a concern that risk may be underestimated.
- Consider a lifetime risk tool (e.g. QRISK3-lifetime) to inform discussions on CVD risk and to motivate lifestyle changes, particularly for people with a 10-year score < 10%, and people < 40 who have CVD risk factors.

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 include, but not limited to the following group of people;

- obesity increases CVD risk (NICE CG189)
- treated for HIV
- severe mental illness
- taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
- already taking medicines to treat CVD risk factors
- 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 not already in the risk calculator).

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 those aged 18 to 40 with type 1 diabetes, including those who have had diabetes for ≤ 10 years

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 target 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

Statins in Pregnancy and Lactation

Statins should be stopped 3 months before attempting to conceive and not be restarted until breastfeeding is finished. Stop statins if pregnancy is a possibility.

ABBREVIATIONS

ALT: alanine aminotransferase
AST: aspartate aminotransferase
CHD: coronary heart disease
CKD: chronic kidney disease
CVD: cardiovascular disease
FH: familial hypercholesterolaemia
JBS: Joint British Societies
LDL-C: low density lipoprotein cholesterol
non-HDL-C: non-high density lipoprotein cholesterol
PCSK9i: proprotein convertase subtilisin kexin 9 monoclonal antibody inhibitor
QOF: Quality and Outcomes Framework
SLE: systemic lupus erythematosus
SPC: summary of product characteristics
TC: total cholesterol

EXTENT OF LIPID LOWERING WITH AVAILABLE THERAPIES

Approximate reduction in LDL-C					
Statin dose mg/day	5	10	20	**40**	**80**
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin + Ezetimibe 10mg		52%	54%	57%	61%

Low intensity statins will produce an LDL-C reduction of 20-30%

Medium intensity statins will produce an LDL-C reduction of 31-40%

High intensity statins will produce an LDL-C reduction above 40%

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

- **Rosuvastatin** may be used as an alternative to atorvastatin if compatible with other drug therapy. Some people may need a lower starting dose (see BNF).
- Low/medium intensity statins should only be used if intolerance or drug interactions.
- **Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C or LDL-C than doubling the dose of the statin.
- **PCSK9i** (NICE TA393, TA394) alone or in combination with statins or ezetimibe produce an additional LDL-C reduction of approximately 50% (range 25-70%).
- **Bempedoic acid** when combined with ezetimibe (TA694) produces an additional LDL-C reduction of approximately 28% (range 22-33%).
- **Inclisiran** (TA733) alone or in combination with statins or ezetimibe produces an additional LDL-C reduction of approximately 50% (range 48-52%) but no clinical outcome evidence is currently available.

MONITORING

Baseline Measurements

In addition to full lipid profile, measure renal, thyroid and liver profiles (including albumin) and HbA1c to exclude secondary causes and co-morbidities.
Measure baseline liver transaminase (ALT or AST) before starting a statin.
Measure CK if unexplained muscle pain before starting a statin.
CK should not be measured routinely especially if a patient is asymptomatic.

	Primary Prevention		Secondary prevention	
	Lipid Profile	ALT or AST	Lipid Profile	ALT or AST
Baseline	✓	✓	✓	✓
2-3 months	✓	✓	✓	✓
6-9months	If targets are not met, and up-titration is agreed, repeat full lipid profile and ALT or AST within 2-3 months of each up-titration of statin dose or addition of ezetimibe as required			
12 months	✓	✓	✓	✓
Yearly	✓*		✓*	

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, lifestyle modification and address CVD risk factors.

**Offer in secondary prevention, and consider in primary prevention 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.
Do not stop statins because of an increase in blood glucose level or HbA1c

Advise that the risk of muscle pain, tenderness or weakness associated with statins is small and the rate of severe muscle adverse effects (rhabdomyolysis) is extremely low.

Liver Transaminases

Measure liver transaminase within 3 months of starting treatment and then within 2-3 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:

- Do not routinely exclude from statin treatment
- 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.

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
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NICE 2021. TA694 www.nice.org.uk/guidance/TA694
NICE 2021. TA733 www.nice.org.uk/guidance/TA733
NICE 2022. TA805 www.nice.org.uk/guidance/ta805
NICE 2023. NG238 www.nice.org.uk/guidance/ng238
NICE 2023. CG189 www.nice.org.uk/guidance/cg189

TITRATION THRESHOLD / TARGETS

	NICE titration threshold / QOF	JBS3**
Primary prevention	Escalate lipid lowering therapy if non-HDL-C reduction from baseline ≤ 40%	non-HDL-C <2.5mmol/L (LDL-C <1.8mmol/L)
Secondary Prevention	Aim for an LDL-C of ≤ 2.0 mmol/L, or non-HDL-C of ≤ 2.6 mmol/L at least*	
FH	Optimise lipid lowering therapy to achieve at least 50% reduction in LDL-C (or non-HDL-C.)	

*Consider ezetimibe to reduce CVD risk further, even if the NICE lipid target for secondary prevention of CVD is met.

**LDL-C and non-HDL-C levels should be reduced as much as possible in people with CVD. Consider a personalised target, as clinically indicated, e.g. 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 and fasting LDL-C thresholds are summarised below.

NICE TA393 Alirocumab **NICE TA394 Evolocumab**	Without CVD	With CVD	
		High risk [1]	**Very high risk [2]**
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL C > 4.0 mmoL/L	LDL C > 3.5 mmoL/L
Primary heterozygous-FH	LDL C > 5.0 mmoL/L	LDL C > 3.5 mmoL/L	

[1] History of any of the following: ACS; coronary or other arterial revascularisation procedures; CHD, ischaemic stroke; PAD. [2] Recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).

Bempedoic acid/ezetimibe and inclisiran are available in primary care and do not require initiation by specialist services.' PCSK9i may be available for prescribing in primary care: see local initiation pathways.

TRIGLYCERIDES

Triglyceride concentration	Action
Greater than 20mmol/L	**Refer to lipid clinic for urgent specialist review** if not a result of excess alcohol or poor glycaemic control. At risk of acute pancreatitis.
10 - 20mmol/L	Repeat the TG measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and review for potential secondary causes of hyperlipidaemia. Seek specialist advice if the TG concentration remains > 10mmol/litre. At risk of acute pancreatitis
4.5 - 9.9mmol/L	If non-fasting triglycerides are greater than 4.5mmol/L, repeat with a fasting TG measurement Be aware that the CVD risk may be underestimated by risk assessment tools, optimise the management of other CVD risk factors present and seek specialist advice if non-HDL-C concentration is > 7.5 mmol/litre.

Icosapent ethyl (TA805)

- Check fasting triglycerides levels.
- Manage secondary causes of hypertriglyceridaemia.
- Consider icosapent ethyl (TA805) if patient has established cardiovascular disease (secondary prevention) **and**
  - on statins and fasting TG ≥ 1.7mmol/L and LDL-C* between 1.04‡ and ≤2.6mmol/L
- See table above and refer as appropriate.

* LDL-C cannot be calculated using Friedewald's formula if TG >4.5. Discuss with your lab. Consider using an alternative equation (eg Sampson, doi: 10.1001/jamacardio.2020.0013) or beta-quantification.

‡ labs don't report calculated LDL-C beyond one decimal point

STATIN INTOLERANCE

Statin intolerance is defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in adherence to therapy being compromised.

For people who are intolerant of the recommended statin treatment see the NHSE AAC statin intolerance algorithm, available on the NHSE AAC page (Click here)

This document is adapted from 'Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD' Authors: Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. Updated by NHSE Cholesterol Expert Advisory Group.
Approved: June 2025. Review date: June 2026.

Appendix 1: Supporting Clinical information and useful links for Lipid management

1. Lipid Guidance: Supporting Clinical information - https://cks.nice.org.uk/topics/lipid-modification-cvd-prevention/
2. Bempedoic acid in the management of hyperlipidemia – https://www.nice.org.uk/guidance/ta694
3. Inclisiran in management of hyperlipidaemia - https://www.nice.org.uk/guidance/ta733
4. Cardiovascular disease prevention: Lipid management including access to inclisiran - NHS England » Cardiovascular disease prevention: Lipid management including access to inclisiran
5. Funding and supply of inclisiran (Leqvio®) - NHS England » Funding and supply of inclisiran (Leqvio®)
6. Icosapent ethyl in management of hyperlipidaemia - https://www.nice.org.uk/guidance/ta805
7. Lipid management e-tool - Lipid management tool - Health Innovation Yorkshire & Humber
8. Statin intolerance - NHS Accelerated Access Collaborative » Statin intolerance pathway
9. Should I take a statin? NICE shared decision making tool https://www.nice.org.uk/guidance/ng238/resources/patient-decision-aid-on-should-i-take-a-statin-pdf-243780159
10. QRISK 3-lifetime CVD risk calculator - QRISK3-lifetime
11. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials - PubMed
12. UCL Partners proactive care frameworks - The Proactive Care Frameworks - UCLPartners