Information for Clinicians

Department of Clinical Biochemistry

Assessment and Management of Lipids in Primary Care

Lipid requests

In most people Cholesterol, HDL and Non-HDL measurement is used for screening and monitoring. Non-HDL cholesterol is used as an estimation of the total number of atherogenic lipoprotein particles; it is used to risk stratify patients and as a treatment target.

- Primary prevention target aims for a 40% reduction in Non-HDL.
- Secondary prevention targets aim for Non-HDL less than 2.5mmol/L

When are full lipid profiles required?

NICE CG181 states that a full lipid profile should be requested at least once before starting therapy. This should include Cholesterol, HDL, Non-HDL, LDL-c and Triglycerides. It does not need to be fasted.

Ensure a full lipid profile is requested:

- At least once before starting treatment
- In known hypertriglyceridaemia
- With mixed hyperlipidaemia of genetic aetiology
- When low HDL noted
- With risk factors for high triglycerides such as poorly controlled diabetes, alcohol excess or medications

Familial Hypercholesterolaemia

- Familial Hypercholesterolaemia (FH) is common with an estimated prevalence of 1 in 250.
- This condition should be considered and patients referred if they have:
  - total cholesterol (TC) >7.5 mmol/L or LDL-cholesterol >4.9 mmol/L.
  - **AND** a family history of premature coronary heart disease in a 1st degree relative (defined as <60 years old) or a 2nd degree relative (defined as <50 years old).
- We would also recommend referral in patients with a TC >9.0 mmol/L or a non-HDL cholesterol >7.5 mmol/L even in the absence of a family history of premature coronary heart disease.
- The lipid clinic will decide on the likelihood of FH and if suspected arrange appropriate genetic testing to confirm/exclude this diagnosis. If confirmed appropriate family cascade testing can be initiated by the clinic.

- In patients in whom Familial Hypercholesterolaemia (FH) is suspected do not use QRISK to decide on treatment, this will underestimate the true level of risk. It is in most instances reasonable to wait for patient to be seen in clinic before starting treatment.
- If a patient is started on treatment prior to being seen in clinic, please ensure that at least one full lipid profile has been requested beforehand.
- In general, the target for treatment is to lower the LDL by at least 50%

Mixed dyslipidaemias (raised cholesterol and raised triglycerides)

- Mixed dyslipidaemias are common. These patients have a total cholesterol >5.0mmol/L and raised triglycerides. This type of dyslipidaemia, is often observed in patients who are obese/overweight, are insulin resistant/have glucose intolerance or who consume alcohol in excess. In many instances this type of dyslipidaemia is very amenable to lifestyle intervention.

- However, advice should be sought if a patient with a mixed dyslipidaemia has a personal or family history of premature cardiovascular disease. These patients may have Familial Combined Hyperlipidaemia (FCH), which is an autosomal dominant inherited condition associated with an increased risk of cardiovascular disease.

- QRISK should also **NOT** be used to assess CV risk in a patient with suspected FCH

Hypertriglyceridaemia

- If triglycerides are >20 mmol/L consider urgent discussion with a lipid consultant. These patients may require immediate initiation of a Fibrate and urgent referral to secondary care. There is a significant risk of pancreatitis.
- If the triglyceride concentration is between 10-20 mmol/L repeat a full lipid profile (after an interval of 5 days but within 2 weeks). Please refer to the lipid clinic if triglycerides are >10 mmol/L on more than one occasion.
- In all cases of hypertriglyceridaemia consider alcohol, obesity, diabetes, diet and medication as common possible causes.

Summary of lipid management for Primary and Secondary Prevention

- All patients with raised cholesterol should be encouraged to eat a diet high in fruit, vegetables & wholegrains and low in saturated fat (saturated fat increases total and LDL cholesterol).

- Those with diabetes should optimise their control and overall calorie consumption.
- Encourage physical activity: 150 mins moderate aerobic activity a week.
- See https://www.nhs.uk/live-well/

A general outline for the approach to managing patients is shown in the flow chart below, this is a national pathway which can be found at:
http://www.bswformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=2&SubSectionRef=02.12&SubSectionID=A100&drugmatch=5759#5759

- A statin intolerant pathway can be found on the same link

Liver Function

- Do not exclude statin treatment for people whose baseline ALT or AST levels are raised but are <3 x the upper limit of normal (ULN)
- Monitor liver function at 3 and 12 months after starting statin only
- Stop statin if ALT >3 x ULN

Creatine Kinase

- Only measure a baseline CK if the patient has myalgia. If CK levels are more than 5 x upper limit of normal do not start statin treatment, investigate and refer as necessary
- Do not routinely measure CK in treated asymptomatic patients. If it is necessary to measure CK and levels are raised but <5 x the upper limit of normal, either stop or reduce to a lower dose of statin once symptoms have resolved
- If CK levels are >5 x upper limit of normal, then stop statin immediately and refer to BNF

Referral to Lipid Clinic

- Common secondary causes of dyslipidaemia (such as excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome) should be excluded before referral.
- In general, a referral should only be made if a patient's dyslipidaemia persists after treatment of secondary causes and 3 months targeted management of adverse lifestyle/metabolic features.
- On referral we would ask that the following tests have been ordered: HbA1c, TFT, U&E, LFT, Lp(a) and urine albumin creatinine ratio.
- The referral should include recent lipid profile, a full list of current medications, BMI, cardiovascular risk factors and family history.
- Any letter for advice or referral should be sent through the choose and book service eRS system

Please refer the following groups of patients:

- Suspected Familial Hypercholesterolemia (FH)
- Severe hypertriglyceridemia (1x triglycerides >20 mmol/L, 2x >10 mmol/L)
- Some groups of patients with lower levels triglycerides than above benefit from being seen if they require behaviour modification.
- Intolerance to medications; please see statin intolerant pathway below
- Severe hypercholesterolemia (TC >9 or non-HDL-C >7.5 mmol/L)
- Patients who may be suitable for injectable Alirocumab or Evolocumab therapies in accordance with NICE Guidance (TAs 393 and 394)
    - FH without CVD but LDL-C persistently above 5 mmol/L
    - FH with CVD and LDL-C persistently above 3.5 mmol/L
    - Non-FH but *high or **very high risk of CVD with LDL-C persistently above 4 or 3.5 mmol/L respectively
      (*High risk of CVD = disease in one vascular territory)
      (**Very high risk of CVD = disease in two vascular territories or progressive disease despite lipid lowering treatment)

Pregnancy

Lipid-lowering medication is not recommended for 3 months prior to conception, during pregnancy, nor during breastfeeding.

Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD

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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

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

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 statin treatment.
Atorvastatin 20mg daily

- Measure full lipid profile again 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
  - 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 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 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**.
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 angina, previous MI, 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.
Prescibe 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/1.73m²).

- Measure full lipid profile again 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 started on less than atorvastatin 80mg and the person is judged to be at higher risk (based on comorbidities, risk score or clinical judgement - see page 2 *'Additional Risk Factors'*), consider increasing to 80mg atorvastatin. 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 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 control non-HDL-C/LDL-C well enough after 3 months confirm statin adherence, then consider the following options based on shared decision making* with the patient

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 > 2.5mmol/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 > 2.5mmol/L; consider **injectable therapies** arrange a fasting blood test and assess eligibility

Injectable therapies**
If non-HDL-C > 2.5mmol/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 are not met, consider **ezetimibe 10mg daily** (if not previously considered)

* See overleaf for information to support shared decision making

** 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. If 40% reduction of non-HDL-C 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. 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 m² 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 groups of people;
- severe obesity (BMI>40kg/m²) 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 RLE, 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/1.73m² 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/1.73m² or more.

Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m²

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
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%) but no clinical outcome evidence is currently available.
- **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	✔	✔	✔	✔
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	✔	✔	✔	✔
Yearly	✔*		✔*	

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, 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 <2.6mmol/L (LDL-C <1.8mmol/L)
Secondary Prevention	Optimise lipid lowering therapy to achieve at least 50% reduction in LDL-C (or non-HDL-C.)	
FH		

If baseline cholesterol is unknown in the setting of secondary prevention use the use 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 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.

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)

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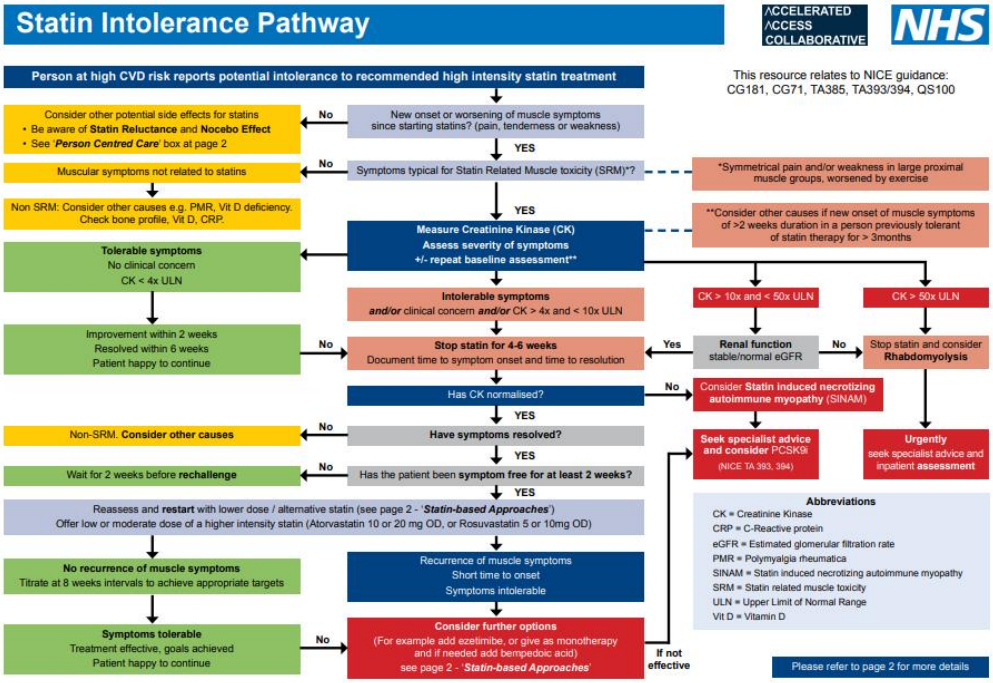

Introduction

- 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 PCSK9i 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 regular review helps addressing concerns around medicine safety and underline the importance of adherence.

(1) **Nocebo effect** is negative expectations of the patient regarding a treatment leading to reporting more negative effects even if they are prescribed a placebo.
(2) **Statin reluctance** is an attitudinal state of aversion to taking statins (often without prior 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 patient.
- Switch to a different statin or re-challenge with the same statin using a lower dose or frequency (intermittent dosages)
- Patients who do not tolerate statins on a daily basis, alternate day or twice-weekly 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 the above approaches but any reduction of LDL-C / non-HDL-C is beneficial.

LDL-C lowering options for patients with genuine statin intolerance

- 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 algorithm
- 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 further 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 2023
Pathway approved by NICE July 2021. Please refer to the Lipid Management Pathway and Full List of References (click here)

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