South West London Integrated Care System

Lipid Management Guidance: Adult Medicines Optimisation pathways

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Abbreviations used in this guideline:

TC= total cholesterol, TG= triglycerides, HDL-C= high density lipoprotein-cholesterol, LDL-C= low density lipoprotein-cholesterol, non-HDL-C= non-high-density lipoprotein- cholesterol
Non-HDL-C = total cholesterol- HDL cholesterol, LLT= lipid lowering therapy; HI statin=High intensity statin; TFTs=Thyroid function tests; A+G= Advice and guidance

Definition of statin intolerance (NICE 2015):

Statin intolerance is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy

Please note: These pathways have been developed for use in adult patients in SWL and this guidance does not override the individual responsibility of healthcare professionals (HCPs) to make decisions appropriate to the circumstances of the individual patients, in consultation with the patient and/or guardian or carer

Contra-indications for all pathways: the lipid management treatments listed are not recommended in patients who are pregnant or breastfeeding and in the 3 months prior to conception. Please check individual summary of product characteristics (SPC) for each medication and consider contra-indications before prescribing.

For further information on SWL formulary status (RAG rating) of specific drugs, please refer to the SWL Network Joint Medicines formulary

Primary Prevention: Medicines Optimisation for Lipid Management in primary care

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Please note: Lifestyle changes and dietary measures are key to CVD event reduction together with drug therapy (see page 7)

In primary care check: bloods (non-fasting full lipid profile: (TC, TG, HDL-C, LDL-C, non-HDL-C) liver function (LFTs), HbA1c (manage/review diabetes mellitus (DM) if ≥48mmol/mol), thyroid & renal function (and albumin creatinine ratio when applicable), blood pressure (BP), weight, body mass index (BMI), alcohol intake, smoking status and **calculate CV risk. Use** QRISK3 wherever possible or QRISK2 score using EMIS/in-built system template in people up to and including aged 84 years. Interpretation of CVD risk scores should always reflect informed clinical judgement. Consider secondary causes of hyperlipidaemia and manage as needed, consider if lipid profile may indicate FH- (*see pages 4 and 13). If non-fasting Triglycerides above 4.5mmol/L, please refer to page (Hypertriglyceridaemia pathway- see page 12)*

Offer **high intensity statins (e.g. atorvastatin)** to all patients with high CVD risk including:
1. Type 2 DM with CVD risk ≥ 10% and/or chronic kidney disease (CKD). Do not use a risk assessment tool (QRISK 3) to assess cardiovascular disease (CVD) risk in people with an eGFR less than 60 ml/min/1.73 m2 and/or albuminuria (QRISK3 has updated to eGFR<30ml/min/1.73m^2).
2. Familial hypercholesterolaemia, or CKD and/or albuminuria, or type 1 DM and **age above 40 years** or **DM over 10 years** or **nephropathy** or with **other CVD risk factors** *NICE[6]*

Consider additional CVD risk factors, if present, together with QRISK score:
Severe obesity (BMI >40kg/m^2), socio-economic status, human immunodeficiency virus (HIV) treatment, migraine, erectile dysfunction, severe mental illness, medications that may cause dyslipidaemia (e.g. antipsychotics, corticosteroids, immunosuppressants), autoimmune and inflammatory disorders e.g. systemic lupus erythematosus (SLE), impaired fasting glycaemia, hypertriglyceridaemia (*see page 13*); CV risk changes (BP, smoking status and lipid levels)

Consider options with **shared** decision making (*page 7-8*), education and lifestyle interventions (page 7) to **modify CVD risk (e.g. BP, HbA1c, weight, smoking, alcohol intake, diet, physical activity).** For all patients consider the risk: benefit of therapy holistically and consider **deprescribing options** e.g. frailty, short estimated life expectancy over next 5 years, poor overall functional status, low CV event risk, suspected adverse effects related to medication, non-adherence- a shared management plan with the patient and carer/family members (SPS guidance; Prescqipp; a guide to deprescribing statins). Optimise blood pressure management and other co-morbidities. Support lifestyle interventions, medicines adherence and ensure regular checks of CVD risks

If age below 85 years and QRISK above 10%: address modifiable risk factors and following a shared decision: consider initiating statin therapy with a **moderate dose** of a **high intensity drug (HI)**: **atorvastatin 20mg daily** (**alternative is rosuvastatin 10mg daily**)* *-see page 7 for high intensity statin comparison table* -consider drug interactions that may affect dosing (see BNF)

After 3 months, check full lipid profile: is non-HDL cholesterol reduction greater than 40% from baseline?
Check adherence to medication, timing of dose, statin adverse effects/intolerance/hesitancy & diet/lifestyle interventions, measure LFTs (ALT)

Yes → **Review annually** for adherence to medications, diet and lifestyle, check required bloods e.g. lipids, LFTs at 12 months post initiation then as clinically indicated. **Refer for support as required from specialist teams**

No →
Step 1: in primary care- Consider up-titration of statin to a maximum dose **atorvastatin 80mg^ (alternative is rosuvastatin 20mg to 40mg)*-** *see HI statin table page 7 and consider dose limitations in CKD (eGFR<30/min^*)*
Step 2: in primary care- If intolerant to higher dose of statin, consider **adding ezetimibe 10mg daily** (SPC- check contra-indications) to maximum tolerated dose of statin
Step 3: in primary care- If intolerant to any statin, **start ezetimibe 10mg daily and/or** consider adding bempedoic acid **[Prescribed as bempedoic acid plus ezetimibe 180mg/10mg (Nustendi)▼]** *Formulary status- Amber 1* (NICE[8]). *Refer to eRS lipid specialist advice and guidance as required* (see page 6- *statin intolerance pathway*)

Yes → **After 3 months, is non-HDL cholesterol reduction greater than 40% from baseline?** Check adherence to medication, adverse effects/intolerance/hesitancy and lifestyle interventions

No → **Refer to lipid clinic for further input**

^ Atorvastatin: consider initial dose of **atorvastatin 20mg-** potential drug interaction; high risk of or experiencing adverse effects; intolerance. For CKD- eGFR less than 30ml/min/1.73m^2- seek specialist advice for dose up-titration
*Rosuvastatin: CrCl 30-60ml/min- initiate a lower dose- see BNF (note: if CrCl less than 30ml/min- specialist input to initiate and up-titrate; use of 40mg dose- specialist supervision advised)

For all drugs listed- check SPC or BNF for cautions, contraindications & interactions

Familial Hypercholesterolaemia (FH) Pathway

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Suspect FH in patients with TC >7.5mmol/L and/or LDL-C >4.9mmol/L and/or non- HDL-C > 6mmol/L

In primary care case find age <30 years:

TC >7.5mmol/L or LDL-C >4.9mmol/L or non-HDL-C >6 mmol/L

In primary care case find age ≥30 years:

TC >9.0mmol/L or LDL-C >6.5 mmol/L or non-HDL-C >7.5mmol/L

In primary care check bloods: repeat lipid profile (TC, TG, HDL-C, LDL-C, non-HDL-C) plus LFTs, TFTs, renal function, HbA1c

If TG > 2.3mmol/L

If TG ≤ 2.3mmol/L

Unlikely FH: Investigate raised triglycerides-TG with a fasting lipid profile (refer if indicated) and aim non-HDL-C reduction greater than 40% (*see primary and secondary prevention pathways: page 3 and page 5*). **Ensure appropriate SNOMED coding in primary care record:** hypertriglyceridemia and/or hypercholesterolaemia, not FH.

Primary care check:

1. Family history: First degree relative MI less than 60 years old, second degree relative MI less than 50 years old
2. Tendon xanthomata

If either are positive refer to lipid clinic for DNA testing of monogenic FH (Simon Broome criteria)

If not confirmed FH

If confirmed FH*: aim LDL reduction greater than 50% AND follow the recommended treatment management pathway for primary or secondary prevention as for non-FH. **Lipid specialists will recommend/ initiate- options:**

1. **High intensity statin** (atorvastatin or rosuvastatin- maximum tolerated doses- *see high intensity statin table on page 7*)
2. Add in **ezetimibe 10mg daily**
3. Add Bempedoic acid - **Prescribed: Nustendi** (bempedoic acid plus ezetimibe 180mg/10mg**)** ▼ (*NICE[8]*) [*Formulary status- Amber1*] if not reaching target/statin intolerance (*see page 6*)
4. Alirocumab/evolocumab or Inclisiran in CVD secondary prevention (***Formulary status-Red***) *[see PCSK9i mAB pathway on page 9 and Inclisiran on page 10]*

Specialist service for monogenic FH: genetic counselling and DNA test for FH mutation and cascade testing for family members if indicated. Available from lipid clinics.

***Ensure correct coding** in primary care record for confirmed FH. SNOMED: familial hypercholesterolaemia: 398036000, homozygous FH 238078005, heterozygous FH 23807900

For all drugs listed- check SPC or BNF for cautions, contraindications & interactions

CVD Secondary Prevention: Medicines optimisation pathway for Lipid Management

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1) **Check baseline bloods** (non-fasting full lipid profile, LFTs, HbA1c, thyroid and renal function)- consider secondary causes of hyperlipidaemia and manage as needed, consider if lipid profile may indicate FH- (see page 4 and page 13)
2) **Offer high dose high intensity statin** therapy with **atorvastatin 80mg^** (**alternative is rosuvastatin 20-40mg**)* to adults with CVD **without delay**: 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)
3) **Support the self-management** (*see page 7*) of modifiable risk factors e.g. smoking, diet, obesity, alcohol intake, physical activity, blood pressure and glycaemic control (HbA1c)[SWL diabetes guidance]

In primary care check: **Is patient on high dose, high intensity statin? atorvastatin 80mg^ (alternative is rosuvastatin 20mg-40mg)* Consider dose adjustments in CKD, drug interactions, intolerance**

Has non-HDL-C reduced by 40% or more from baseline at 3 months *NICE[6]* AND non-HDL-C below 2.5 mmol/L or LDL-C below 1.8 mmol/L JBS3?

Yes

No

For all patients: Discuss with the patient statin choice (page 7, page 8): reinforce lifestyle, dietary measures, suspected adverse effects to medication and adherence. Consider switching to another HI statin/increase statin dose if on suboptimal dose **and/or add ezetimibe 10mg daily** based on risk score, co-morbidities and clinical judgement. Consider the risk: benefit of therapy holistically and consider **deprescribing options** e.g. frailty, short estimated life expectancy over next 5 years, poor overall functional status, low CV event risk, non-adherence- a shared management plan with the patient and carer/family members (SPS guidance; Prescqipp; a guide to deprescribing statins). Check full lipid profile & LFTs after 3 months

Is Non-HDL-C below 2.5mmol/L or LDL-C below 1.8mmol/L JBS3? -Check adherence to medication/lifestyle measures, intolerance to statin (*statin intolerance- see page 6*). If maximum tolerated dose of statin and ezetimibe does not achieve lipid targets as above, consider the following options based on shared decision making with the patient:

Yes

No

Step 1: In primary care- Add ezetimibe 10mg daily SPC to HI statin and/or adjust statin dose. Recheck full lipid profile (TC, TG, HDL, LDL-C), LFTs in 3 months

Is Non-HDL-C below 2.5mmol/L or LDL-C below 1.8mmol/L on maximum tolerated doses of HI statin and/or ezetimibe JBS3?

Yes

No

Step 2: Consider injectable therapies via lipid clinic/A+G- alirocumab/evolocumab (PCSK9i mAB): refer to lipid clinic if LDL-C >4 mmol/L (or LDL-C >3.5 mmol/L with recurrent CVD event or multivascular disease. PCSK9i (*see page 9*)-***Formulary status- Red***

Consider* inclisiran ▼** via A+G or referral to lipid clinic if LDL-C ≥ 2.6 mmol/L and patient not eligible for PCSK9i mAB/other LLTs. ***Formulary status- Red (*see page 10 for details on initiation*)

Step 3: Check fasting lipid profile **and consider icosapent ethyl ▼** if CVD on a statin, LDL-C above 1.04 and ≤ 2.6 mmol/L plus TG≥ 1.7 and < 4.5mmol/L- ***Formulary status- Amber 2*** (*see page 11*)

For Statin intolerance options- (*see page 6*)**:**
- Rechallenge with low-dose alternative statin
- Specialist recommendation of [bempedoic acid plus ezetimibe] ▼ (*NICE[8]*) ***Formulary status- Amber 1***
- Lipid specialist Initiation inclisiran ▼ (*page 10*)- ***Formulary status- Red***

Discuss lipid lowering options with your patient. In SWL, it is recommended to prescribe **high intensity statin with ezetimibe** for at least 3 months before considering other options or referral to lipid clinic (advice and guidance) to consider injectable therapies (LDL-C) and/or to consider oral Icosapent ethyl (TG)

Consider current regimen if well tolerated and review annually- adherence to medications, dietary and lifestyle measures, check required bloods (full lipid profile, HbA1c if indicated, LFTs at 12 months post initiation and then as clinically indicated)

^ Atorvastatin: consider initial dose of **atorvastatin 20mg-** potential drug interaction; high risk of or experiencing adverse effects; intolerance. For CKD- eGFR less than 30ml/min/1.73m^2- seek lipid specialist advice for dose up-titration

* Rosuvastatin: CrCl 30-60ml/min- initiate a lower dose- see BNF, (note: if CrCl less than 30ml/min- specialist input to initiate and up-titrate; use of 40mg dose- specialist supervision advised) (beware of interactions e.g. concomitant use with clopidogrel, max dose 20mg once daily)

For all drugs listed- check SPC or BNF for cautions, contraindications & interactions

Statin intolerance pathway/options if not achieving lipid lowering targets

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In primary care: **Discuss with the patient** if signs and symptoms are statin intolerance or due to a statin reluctance/non-adherence. **Consider that a statin at any dose reduces CV risk-** if a patient cannot tolerate a high intensity statin, aim to treat with a maximum tolerated dose of a statin, but if symptoms persist consider alternative options/specialist (*see below*)

For **Statin Related Muscle** (SRM) **symptoms:** symmetrical pain/weakness in large proximal muscle groups, worsened by exercise. **Measure creatine kinase (CK)*:** if above 4x Upper Limit Normal (ULN) and below 10x ULN with intolerable symptoms: stop statin for 4 to 6 weeks*. If below 4xULN, consider statin dose adjustments or ezetimibe/alternative lipid lowering therapies.

If CK normalises and symptoms have resolved for at least 2 weeks, then rechallenge: Offer a low or moderate dose of HI statin **e.g. atorvastatin 10 to 20mg daily or rosuvastatin 5 to 10mg daily**. Please note: Non-standard dosing may be prescribed by cardiology and lipid specialist clinics e.g. rosuvastatin 5mg weekly or three times a week (*off label use but accepted practice*)

No recurrence of muscle symptoms:
Titrate dose at 8 week intervals to achieve appropriate targets- continue to monitor for symptoms and continue therapy

If recurrence of muscle symptoms: recheck CK* and consider alternative options or add-on therapy if not tolerating statin/ achieving lipid lowering targets:

1) Continue maximal tolerated dose of statin (if not tolerated -stop the statin) if CK below 4x Upper limit normal
2) Add in **ezetimibe 10mg daily** (SPC)- review adherence/tolerance and full lipid profile in 3 months
3) Stop statin for 2 weeks and rechallenge with alternative regimens of HI statins (rosuvastatin 5mg three times a week)

If tolerating ezetimibe but not achieving lipid lowering targets: consider adding bempedoic acid [**Prescribed: bempedoic acid plus ezetimibe 180mg/10mg▼**] (*NICE*[8]) or **lipid specialist input** -inclisiran▼ for secondary prevention

Bempedoic acid initiation: Prescribed- Bempedoic acid plus ezetimibe 180mg/10mg (Nustendi)▼(*NICE*[8])
This is **Amber 1** in SWL and initiation can be undertaken **by a specialist** or prescribed in primary care :

Monitor SPC	Baseline
Renal function	eGFR <30ml/min/1.73m^2: Avoid
Liver function	Severe hepatic impairment: Avoid
Uric acid	Active gout: Avoid
FBC	Hb level (in particular)
Drug interactions	e.g. simvastatin 40mg; For full list- See BNF & SPC
Contraindications	Pregnancy, breast feeding, age <18yrs: For full list- See SPC
Myopathy symptoms	Check

Bempedoic acid primary care monitoring: NOTE: Prescribed- Bempedoic acid plus ezetimibe 180mg/10mg (Nustendi)▼(*NICE*[8])

Monitor SPC	Within 3 months then annually
Renal function	Review- eGFR <30ml/min/1.73m^2- limited experience
Liver function	Review- AST/ALT ≥3x ULN- Stop treatment
Uric acid	Hyperuricaemia with gout symptoms present- Stop
FBC	Hb decrease by ≥20g/L from baseline or < lower limit of normal (LLN)- Stop treatment, investigate further/ refer to appropriate specialist
Myopathy Symptoms	Monitor: if present check CK >10x ULN confirms myopathy- Stop bempedoic acid and statin; reduce statin dose or change statin/lipid lowering therapy if symptoms persist (***see above***). ▼Report any side effects to the yellow card scheme. Patient counselling**^**

Patient information: Report any unexplained muscle pain, tenderness or weakness**^**.

***For muscular symptoms:** check **CK: if >50x ULN** stop statin and consider rhabdomyolysis- *seek urgent specialist advice*, **if 10-50xULN** check renal function- if deteriorating, stop statin for 1 month to see if symptoms and CK resolves. Restart a lower dose and uptitrate or consider alternatives above. **See:** Statin-Intolerance-Pathway-NEW.pdf (england.nhs.uk)

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, Vitamin D, C-Reactive Protein.

For all drugs listed- check SPC or BNF for cautions, contraindications & interactions

Risk factors for intolerance: for all doses of all statins (except for simvastatin 80 mg), factors predisposing to these adverse effects are not well defined, but as with most drugs, older people appear to be more vulnerable. Hypothyroidism, pre-existing muscle disease, and renal impairment are also possible causative factors, and commencement of treatment with an interacting drug is a well-established precipitant. Other suspected risk factors include female sex, diabetes mellitus, and Chinese (and possibly East Asian in general) ancestry.

For abnormal LFTs: If transaminases raised 3xULN stop and restart once LFTs normalised- consider other causes of abnormal LFTs. LFTs are checked at baseline and within 1 year of statin therapy.

Shared decision making concerning lifestyle and statins

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Lifestyle interventions: There are many resources to support behaviour change and self-management e.g. Heart UK and British Heart Foundation, national support groups and local social prescribing options. Support the patient to review their diet, physical activity, weight, smoking, alcohol intake, diabetes care and mental health considerations which are key to lipid management. In dietary intervention studies, CVD events were reduced by 12% over 5 years (NNT=95), and statins/lipid lowering therapies reduce CVD risk by 25% for each year of treatment per 1mmol/L LDL-C reduction -*see table below (Lancet 2016).* Shared decision making: *Numbers needed to treat (**NNT**) and harm (**NNH**) over 5 years of daily high intensity statin therapy (Lancet 2016)*

For **primary prevention-** Consider using a lifetime risk tool such as QRISK3-lifetime to inform discussions on CVD risk and to motivate lifestyle changes, particularly for people with a 10-year QRISK3 score less than 10%, and people under 40 who have CVD risk factors. Please refer to NICE statins patient decision aid to support discussions around statin initiation, benefits and risks.

	NNT		NNH
Primary prevention of major vascular events	20	**New cases of diabetes**	100 to 200
Secondary prevention of major vascular events	10	**Myopathy**	2,000

For 10,000 patients taking a statin for 5 years, achieving 2mmol/L LDL-C reduction: 1000 MVEs avoided (secondary prevention) and 500 MVEs avoided (primary prevention); 100 newly diagnosed diabetes, 5 cases of myopathy and 1 rhabdomyolysis, and <1 active liver disease

MVEs= major vascular events: MI, stroke, coronary revascularisation
Reference: AHA statin safety and associated adverse events, 2019

Lipid management options and LDL reduction: Consider also the evidence of a benefit for CV risk reduction with each medicine (Heart UK- Patient information guide)

	Approximate reduction in LDL-C				
Choice of statin or lipid lowering therapy/ daily dose	5mg	10mg	20mg	40mg	80mg
Fluvastatin *(non-formulary)*			21%	27%	33%
Pravastatin (*consider as a 3rd option statin if atorvastatin and rosuvastatin are inappropriate*)		20%	24%	29%	
Simvastatin		27%	32%	37%	42%*
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53% specialist initiation	
Atorvastatin with Ezetimibe 10mg		52%	54%	57%	61%
Ezetimibe 10mg with Bempedoic acid 180mg	approx. 38%^^				

NB. High intensity (HI) statins reduce LDL-C >40% (*highlighted in green*) and are more effective at preventing cardiovascular events than low/medium intensity statins

NICE/AAC recommends atorvastatin and rosuvastatin as HI statins

***simvastatin 80mg is not recommended due to muscle toxicity risk**

^^17-18% LDL-C lowering for bempedoic acid, ezetimibe 21% approximations vary in current study data.
Ref 12: C.Ballantyne et al; Eur J Prev Cardiol. 2020 Apr;27(6):593-603. doi: 10.1177/2047487319864671

Common and uncommon side effects for statins may be found here: Statins - Side effects - NHS (www.nhs.uk)

For contra-indications please refer to individual summary of product characteristics (SPC) for each medication: women of childbearing age need to ensure adequate contraception during statin treatment and for 1 month afterwards, and statins should be discontinued for 3 months before attempting to conceive (BNF)

Refer to a person centred approach for addressing statin reluctance/hesitancy and potential intolerance: Statin-Intolerance-Pathway-NEW.pdf (england.nhs.uk) and for deprescribing options

Summary of lipid lowering therapy options and CV risk reduction

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Lipid management drug	Indication (NICE)	Administration	LDL lowering effect	CV outcome data	LT safety data
High intensity statin (atorvastatin or rosuvastatin)	Adjunct to diet in hypercholesterolaemia, FH, CV risk reduction: primary and secondary prevention	One tablet daily (oral)	40-50%	Yes (primary and secondary prevention)	Yes
Ezetimibe	With statin to reduce CV risk: primary and secondary prevention, or if statin intolerance, FH	One tablet daily (oral)	24%	Yes (secondary prevention)	Yes
PCSK9i mAB (evolocumab or alirocumab)	FH if LDL>5mmol/L, statin intolerance, CV risk reduction: secondary prevention if LDL>3.5-4mmol/L	SC injection every 2 weeks (can be self administered)	60% +	Yes	Yes
Bempedoic acid	With ezetimibe in statin intolerance	One tablet daily (oral)	28%	Yes (primary and secondary prevention)	Short term safety data from trials of up to 2 years
Inclisiran (PCSK9i)	Secondary prevention if LDL >2.6mmol/L, statin intolerance	SC injection twice a year	52% (48-52%) – ORION 10 and ORION-11 studies	Awaited	Awaited (short-term data of up to 2 years)
Icosapent ethyl	Secondary prevention if LDL-C > 1.0mmol/L and ≤ 2.6mmol/L with fasting TG >1.7mmol/L in combination with statin therapy	Two capsules twice a day (oral) taken with food	- TG lowering effect 18%	Yes (secondary prevention)	Awaited (trial was 4-5 years)

PCSK9 Inhibitors (monoclonal antibodies-mABs) and Lipid Clinic Referral

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If still not achieving targets, or following confirmed statin intolerance, **refer to lipid clinic** for consideration of initiation of PCSK9i (***Formulary status- Red***). NICE eligibility criteria for PCSK9i (alirocumab or evolocumab) are established CVD or familial hypercholesterolaemia:

NICE TA eligibility criteria for PCSK9i	Without CVD	With CVD and high risk	With CVD and very high risk
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL-C > 4.0mmol/L	LDL-C > 3.5mmol/L
Primary heterozygous FH	LDL-C > 5.0mmol/L	LDL-C > 3.5mmol/L	

High risk: history of ACS, coronary/arterial revascularisation, CHD, ischaemic stroke, PAD

Very high risk: recurrent CVD events or CVD events in multiple beds (polyvascular disease)

Lipid clinic will initiate, monitor and supply a PCSK9i (***Formulary status- Red***), either alirocumab or evolocumab: (*NB. there is no first line PCSK9i in SWL)*

- **ALIROCUMAB** usual starting dose is 75mg subcutaneous (SC) injection once every 2 weeks (or if LDL-C reduction of >60% required, start on 150mg SC injection once every 2 weeks or 300mg SC once every 4 weeks
- **EVOLOCUMAB** 140mg SC injection every 2 weeks (**NOTE**: 420mg every 2 weeks is not licensed/commissioned for these indications. It is available for Homozygous FH treatment and only commissioned by NHS England through dedicated apheresis centres. Lipid specialist to refer patients when clinically appropriate)
- Continue existing oral lipid lowering therapy and assess response within 3 months of initiation.

LDL-C reduction >30% CONTINUED therapy and ongoing review 6-monthly by lipid clinic with a new lipid profile and/or other relevant tests (**PCSK9i mABs*: Formulary status-Red***)
If lipid levels are above national recommended targets for primary or secondary prevention (see page 13): review lifestyle, diet, adherence and other secondary causes for hypercholesterolaemia. Discuss lipid optimisation options with the patient and consider add-on lipid lowering therapies, PCSK9-I dose increase aiming at achieving strategy-specific lipid targets

Intolerance/adverse event- DISCONTINUE therapy and consider alternative lipid lowering options including switch of PCSK9i: lipid clinic to communicate action plan to primary care

LDL-C reduction <30%: check adherence and injection technique
Consider uptitration of dose/alternative lipid lowering options (e.g. Inclisiran in CVD) if inadequate response persists with PCSK9i (see page 8)
Based on current clinical practice, switch between PCSK9-I therapy may be considered in rare, but specific clinical scenarios (e.g. a change in patients' CV risk; a borderline LDL reduction of 30% is thought to be related to neutralising antibodies)
Lipid clinic to communicate lipid management plan to primary care.

Please ensure that, prior to referral to lipid clinic, patients have potential secondary causes of hyperlipidaemia excluded such as uncontrolled diabetes mellitus, obesity, excess alcohol consumption, untreated hypothyroidism, proteinuria and some medications, for example, thiazide diuretics and ciclosporin:

Please note that Inclisiran also inhibits PCSK9 production by interfering with RNA (which reduces LDL-C cholesterol levels), but has differing NICE eligibility criteria and may be initiated on the advice of lipid specialists and administered in secondary care/lipid clinics (further information available for clinicians on page 10)

*PCSK9 inhibitor prescribing outside of the guidance recommendations is not commissioned and will require completion of an Individual Funding Request (IFR)

Inclisiran ▼ for CVD secondary prevention

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NICE criteria:

- Inclisiran is recommended for primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults only if:
  - History of cardiovascular disease i.e., ACS, coronary/arterial revascularisation, CHD, ischaemic stroke or peripheral arterial disease (PAD) and
  - Persistent LDL-C levels ≥2.6 mmol/l despite having the maximum tolerated lipid-lowering therapy (HI statins and/or ezetimibe) i.e.
    - Maximum tolerated statins with or without lipid lowering therapies or,
    - Other lipid lowering therapies when statins are not tolerated or are contraindicated
- NOT recommended for primary prevention (no history of CV events) unless enrolled in national clinical trial

SWL formulary status: Red

Lipid specialist initiation. Prescribing, administration, follow-up and monitoring in secondary care until alternative service delivery model is agreed

Initiation:

- Measure baseline lipid profile including LDL-C (fasting sample if possible), liver profile and renal profile
- Dose: 284mg subcutaneous injection by health care professional into abdomen, upper arm or thigh: on day 1, at 3 months, and then every 6 months

Monitoring:

- Full lipid profile including LDL-C at 3 months, at 9 months and then annually
- checking adherence to other medications
- Adverse effects/intolerances
- if LDL-C remains ≥ 2.6mmol/L despite Inclisiran therapy for 9 to 12 months following initiation- patient to be reviewed

Cautions/contraindications: Avoid in severe renal impairment (e.g. CrCl <30ml/min) or requiring haemodialysis, severe liver impairment (Child-Pugh class C), pregnancy/breast-feeding and age <18 years

Adverse effects:

- Mild to moderate injection site reactions are transient and resolve: pain, erythema, rash
- Check for side effects/intolerances at each visit as this is a new medication. Report all ADRs to yellow card scheme: https://yellowcard.mhra.gov.uk/

Missed doses: If a planned dose is missed by

- Less than 3 months: administer Inclisiran and continue dosing according to the patient's original schedule.
- More than 3 months: start a new dosing schedule (i.e. on day 1, at 3 months, and then every 6 months)

See SPC or BNF for full information on cautions, contraindications & interactions

Icosapent ethyl ▼ for hypertriglyceridaemia in CVD secondary prevention

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- Mechanism of action not fully understood, most likely multi-factorial including improved lipoprotein profile with reduction of triglyceride- rich lipoproteins
- Added to maximally tolerated statin for reducing the risk of cardiovascular events in people with raised triglycerides
- NICE recommends for:
  - Adult patients with established cardiovascular disease e.g. ACS (MI or unstable angina needing hospitalisation), coronary/arterial revascularisation procedures, CHD (stable angina), ischaemic stroke/TIA or peripheral arterial disease (PAD) with LDL-C levels > 1.04mmol/L and ≤ 2.60 mmol/L AND fasting triglycerides ≥1.7mmol/L, despite having the maximum tolerated lipid-lowering therapy (HI statins) **in combination with a statin**. If intolerant to statins then NICE can not make any recommendations (outside its marketing authorisation)
- **NOT recommended by NICE** for **primary prevention** (**no history of CV events**):
- Patients with no available LDL-C levels due to high triglycerides (TG>4.5mmol/L) should be discussed with the lipid clinic via advice and guidance.
  - Consider diabetes-related hypertriglyceridaemia and treat as appropriate [refer to the SWL Diabetes guidelines for detailed clinical information]
- **SWL formulary status: Amber 2.** Prescribing, monitoring and stabilisation by lipid specialist for 3 months followed by primary care prescribing according to NICE specifications above. Referrals to be made to their local lipid clinic or via lipid advice and guidance on electronic referral system (eRS)
- **Dosage**: Two 998 mg capsules twice daily taken with food
- **Adverse effects**: Bleeding, Peripheral oedema, Atrial fibrillation/flutter, constipation, musculoskeletal pain, gout and rash (see table for monitoring and follow-up)
- ***Caution:*** *clinicians should balance benefits vs risks on patient individual basis, especially if on DAPT/triple therapy post ACS or PCI. Consider referral to lipid specialist if therapy is required before the cessation of DAPT or triple therapy following ACS*
- **Drug interactions:** No interactions were observed in trials with omeprazole, rosiglitazone, warfarin and atorvastatin (drugs metabolised by the cytochrome P450 enzymes)
- REDUCE-IT trial showed a significant 25% reduction in the primary composite CV outcome (CV death, nonfatal myocardial infarction (MI), stroke, coronary revascularization, or unstable angina) for Icosapent ethyl vs placebo. ARR=4.8%, RRR=22%, NNT=21

Monitor SPC	Baseline	3months/Annually
Renal function	No dose adjustments required. Consider baseline renal function for patients with bleeding risk	Consider repeat renal function for patients with bleeding risk and annually as clinically indicated.
Liver function	LFTs before initiation. Severe hepatic impairment: Avoid	3 months: ALT/AST- if LFTs ≥3x ULN- Stop treatment; Check LFTs periodically thereafter as clinically indicated
Uric acid	Active gout: Avoid History of gout: risk vs benefit ratio	Hyperuricaemia with gout symptoms present- Stop
FBC	Hb level (in particular) and urea	Hb decrease by ≥20g/L from baseline or < lower limit of normal (LLN)- Stop treatment, investigate further
Cautions	Patients with fish/shellfish allergies, hepatic impairment, atrial fibrillation/flutter (greater incidence if previous history of AF) ; bleeding risk (especially if co-prescribed with antiplatelets and anticoagulants- avoid in patients prescribed dual antiplatelets or an antiplatelet with an anticoagulant- refer to CRUSADE score for post-MI bleeding risk or ORBIT bleeding risk score for AF to assess individual risk: benefits) For full list- See BNF & SPC	
Contraindications	Pregnancy, breast feeding, hypersensitivity to soya or peanuts. For full list- See SPC	
Adverse effects and counselling	**Patient information:** awareness of palpitations, dizziness and bleeding risk and signs- need to report; adherence support. **Pulse checks** are also recommended at each review to identify potential AF, to refer for ECG as indicated and to manage associated stroke risk if AF is diagnosed. See SPC for full list. Signpost patients to **Heart UK resources on Triglycerides**	Check intolerances at each visit; See SPC and report any adverse effects to MHRA; In order for this medication to be effective it must be taken as prescribed and so adherence and tolerability should be monitored at each review. If patients cannot take 2 capsules twice a day then STOP therapy.

For all drugs listed- check SPC or BNF for cautions, contraindications & interactions

Hypertriglyceridaemia Pathway

SNOMED code: hypertriglyceridemia 302870006

NHS South West London

Suspected hypertriglyceridaemia: check dietary and lifestyle factors, non-fasting lipid profile (TC, TG, HDL-C, LDL-C, non-HDL-C) plus LFTs, TFTs (TSH, T4), renal function, HbA1c

STEP 1: Consider and exclude secondary causes:
Poorly controlled/new diabetes, excess alcohol intake, non-alcoholic fatty liver, liver disease, obesity (weight/BMI, waist circumference), renal disease (e.g. CKD3) , drug-induced Cushing's, TG-raising medication (e.g. steroids), untreated hypothyroidism (e.g. TSH>10), smoking

→ **Manage lifestyle factors and address secondary causes. Refer to social prescribing and support from local services prior to referral to lipid clinic**

STEP 2: In primary care or secondary care check bloods: repeat fasting (12 hours) lipid profile (TC, TG, HDL-C, LDL-C, non-HDL-C) plus LFTs, TFTs, renal function, HbA1c after 3 months.
Offer lifestyle and dietary changes (physical activity, smoking cessation, reduced alcohol intake, Mediterranean diet). Note: LDL-C levels are not available or reliable if TG levels are above 4.5mmol/L

If fasting TG above 20 mmol/L

-Strict low fat diet, start fenofibrate* and/or Omega 3-fatty acids (if secondary causes excluded)

-**Refer to lipid clinic for urgent specialist review if not a result of excess alcohol or diabetes.** At risk of risk of acute pancreatitis (check for symptoms)

-Omega 3-fatty acids may be initiated by lipid specialists for the control of triglycerides, but are not recommended for the secondary prevention of MI

If fasting TG 10-20 mmol/L

Repeat fasting lipid profile within 2 weeks *plus*

Repeat QRISK3 AND review for potential secondary causes of hyperlipidaemia

If fasting TG remains above 10mmol/L: **Refer to lipid clinic (at risk of pancreatitis). Start a HI statin or a fibrate until lipid clinic review.** Manage other cardiovascular risks, lifestyle and dietary factors, medicines adherence.

If non-fasting 4.5 to 9.9 mmol/L

Repeat with a fasting lipid profile

^CVD risk may be underestimated by risk assessment tools^

Optimise management of other CVD risk factors AND seek specialist advice if non-HDL-C >7.5mmol/L

CVD risk (QRISK3) <10%: consider a fibrate* and recheck lipid levels within 4-6 weeks of initiation. Review ongoing management, aiming for TG <4.5mmol/L and consider de-prescribing if clinically appropriate

Seek lipid specialist opinion via advice and guidance if fibrate is contraindicated or not tolerated. **Refer to lipid clinic if non-HDL > 7.5mmol/L OR If inadequate response to initial treatment**

If fasting TG above 2 to less than 4.5 mmol/L

Primary prevention

Mixed dyslipidaemia and family history: Consider statin if as QRISK underestimate CVD risk

CVD risk (QRISK)>10%: consider a HI statin with atorvastatin 20mg daily for primary prevention (see page 3)

CVD risk (QRISK)<10%: manage any secondary causes of hyperlipidaemia (see above) & CV risks with lifestyle interventions (see page 3)

Secondary prevention

Ensure patient is on maximum tolerated HI statin dose and/or ezetimibe

Patients on HI statins *plus* LDL 1.04-2.6 mmol/L AND fasting TG≥1.7mmol/L

Consider **Icosapent ethyl – Formulary status amber 2****

Two 998mg capsules twice daily *see page 11*

***In single randomised clinical trials, fibrates were not associated with significant reduced cardiovascular outcomes therefore are reserved for treatment of hypertriglyceridaemia or for patients who cannot tolerate other lipid lowering therapies.
First line: Fenofibrate slow-release 160 mg OD (Seek lipid service advice and guidance or use 67 mg OD if eGFR <60)
Monitor renal function (at 3months then annually) and liver function (every 3 months for first year then annually) with fibrate prescriptions; Discontinue: if Cr increase >50% (adjust dose as per SPC) and if AST/ALT >3xULN; Check CK if muscular symptoms: The combination of fibrate with statin increases risk of myopathy

Diabetes-related hyperlipidaemia→ Optimise diabetes treatment: Please refer to SWL Diabetes guidance

****IN PATIENTS WITH A CVD HISTORY AND FASTING TG>1.7mmol/L (or non-fasting TG>2.1mmol/L) and LDL-C 1.04 to 2.6mmol/L, lipid and diabetes specialists may consider adding Icosapent Ethyl ▼ to HI statin therapy (NICE ta 805) See page 11**

For all drugs listed- check SPC or BNF for cautions, contraindications & interactions

Recommended Criteria For Referral to Lipid Clinic

NHS South West London

Hospital lipid clinic	**Referral Criteria:** Please exclude and manage secondary causes before referral to lipid clinic (more details below and on page 12)
Severe hypercholesterolaemia	Persistently elevated cholesterol >9.0 mmol/L (or non HDL-C > 7.5 mmol/L) regardless of existing heart disease / family history
Suspected familial hypercholesterolaemia (FH)	Cholesterol >7.5 mmol/L and LDL-C >4.9 mmol/L AND • Premature CVD (age <60yrs) in the patient OR • Family history: 1st degree relative MI < 60 years old , 2nd degree relative MI <50 years old OR • Presence of tendon xanthomata
Family screening	Cascade screening from identified patient with familial hypercholesterolaemia with a genetic diagnosis of FH
Severe Hypertriglyceridemia	• Triglyceride > 20 mmol/L OR • Triglyceride 10 - 20 mmol/L which persists on a fasting lipid profile (2 samples 1 week apart) OR • Triglyceride 4.5 - 9.9 mmol/L WITH non-HDL cholesterol > 7.5 mmol/L
Statin intolerance	Intolerance of 3 or more statins OR Severe adverse reaction to one statin AND not meeting target LDL-C/ Non HDL-C on ezetimibe 10mg daily
Secondary prevention of CVD	Unable to meet target reductions in LDL-C or non HDL-C despite maximal doses of statins and ezetimibe

The aim of hospital lipid clinics is to focus on patients with primary hyperlipidaemia, please exclude secondary causes before referral:

- For hypercholesterolaemia **exclude** hypothyroidism (check TSH), chronic renal disease or nephrotic syndrome, variant diets (zero carbohydrate; protein supplements)
- For hypertriglyceridaemia **exclude** new/uncontrolled diabetes (check HbA1c) and excess alcohol intake
- For suspected familial hypercholesterolaemia **exclude** secondary causes before referring to the hospital based lipid clinic

LIPID LOWERING TARGETS:

Strategy/Guidance	NICE target	JBS3 target	ESC target
Primary prevention	40% non-HDL-C reduction from baseline	-	LDL-C <3 in moderate risk and <2.5mmol/L in high-risk patients
Secondary prevention	40% non-HDL-C reduction from baseline	Non-HDL-C <2.5mmol/L (LDL-C <1.8mmol/L)	LDL-C <1.8mmol/L (LDL-C target < 1.4 for recurrent ACS and very high-risk groups)
Familial Hypercholesterolaemia	At least 50% reduction in LDL-C from baseline (LDL-C <5mmol/L)	-	LDL-C <1.8mmol/L

- If baseline cholesterol is unknown, aim for Non-HDL-C/LDL-C reduction below the target for the strategy appropriate to the patient
- Joint British Societies' consensus recommends a 'lower is better approach'
- Non-HDL=Total Cholesterol minus HDL-C

References and supporting material

1) **UCLPartners 2023**: Proactive Care framework: Lipid management including Familial Hypercholesterolaemia
2) **NHSE/AAC December 2022:** Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD
3) **NHSE/AAC April 2022:** Statin intolerance pathway
4) **Lancet 2016**; 388:2532-61; R Collins et al; Interpreting the evidence for the efficacy and safety of statin therapy
5) **AHA Scientific Statement 2019**; 39:e38-e81 Statin safety and associated adverse events; Arteriosclerosis, thrombosis and vascular biology
6) **NICE CG181:** Cardiovascular disease: risk assessment and reduction, including lipid modification clinical guideline; July 2014, updated May 2023
7) **NICE CG71:** Familial hypercholesterolaemia: identification and management; August 2008, updated October 2019
8) **NICE TA694:** Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia, Published: 28 April 2021
9) **NICE TA385:** Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia, Published: 24 February 2016
10) **NICETA394:** Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia, Published: 22 June 2016
11) **NICE TA393:** Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia, Published: 22 June 2016
12) **Eur J Prev Cardiol 2020**; Apr 27 (6): 593-603; C. Ballantyne et al; Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy
13) **NICE TA733:** Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia, Published: 06 October 2021
14) **NICE TA805**: Icosapent ethyl for treating Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides, Published 13 July 2022
15) **ESC guidelines on Dyslipidaemias**: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)
13) **Specialist Pharmacy Service**: Cardiovascular disease in older people living with frailty: optimising medicines in multimorbidity and polypharmacy
14) **Tasmania Primary Health**, Australia. A Guide to deprescribing Statins 2019
15) **Heart UK website resources**: What are triglycerides?
16) **SWL Medicines optimisation Committee**: SWL Type 2 Diabetes Mellitus Prescribing guidelines
17) **SWL Medicines optimisation Committee**: SWL Investigation and management of CKD in adults in primary care

Document History

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