Lipid Management: Medicines Optimisation Pathways

South East London (SEL) Integrated Care System

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Developed by SEL Cardiovascular Medicines Working Group on behalf of the SEL Integrated Medicines Optimisation Committee (IMOC) and following guidance from the National Institute for Health and Care Excellence (NICE), NHS England/Accelerated Access Collaborative (AAC) and UCL Partners

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London: South East London Integrated Care System (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

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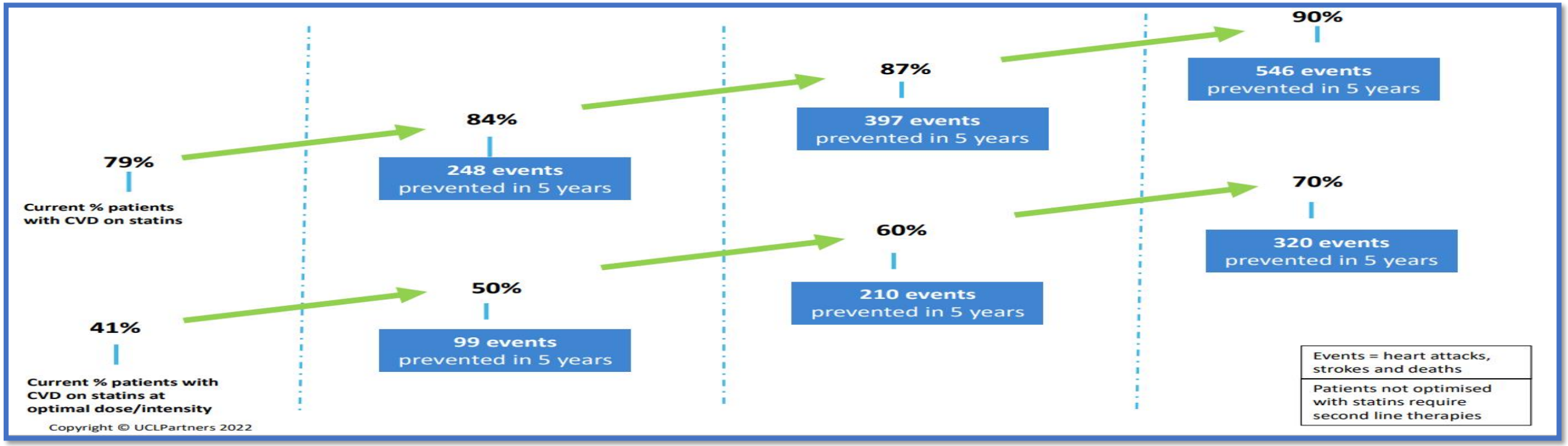
Please note: These pathways have been developed for use in adult patients in SEL and this guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patients, in consultation with the patient and/or guardian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

Why Is Lipid Management Important?

- The UCLPartners search and stratification tools, part of the UCLPartners Proactive Care Frameworks, stratify patients with high impact conditions so that care may be optimised according to clinical priority and capacity (*see links below)*
- Size of the prize- preventing heart attacks and strokes at scale- the number of CV events that could be avoided by optimising lipid management therapy in patients identified in UCLP searches for secondary prevention in an ICS population of 1.7million (*1.9 million population in SEL*):



- *See pages 6 and 15* for a suggested review process in primary care for high risk patients identified in UCLP searches
- UCLPartners Proactive Care Search and Stratification tools- Register here: https://uclpartners.com/proactive-care/search-and-risk-stratification-tools/
- Cholesterol search tool: https://s31836.pcdn.co/wp-content/uploads/Cholesterol-Search-Criteria-July-2022.pdf
- Familial hypercholesterolaemia: https://s31836.pcdn.co/wp-content/uploads/UCLPartners-Search-Tool-%E2%80%93-Familial-Hypercholesterolaemia_2021August.pdf
- It is also important to involve the patient in decision-making in all stages of the lipid management pathways and to consider the risk:benefit of all options (*see pages 8 & 13*)
- Also consider when deprescribing and adherence may be an important consideration for each patient (*see page 4*); Deprescribing statin algorithm: https://www.prescqipp.info/media/4974/attachment-8-statin-algorithm-20.pdf (*registration required*)
- For further information see SEL lipid management webinar: Webinars - South East London CCG (selondonccg.nhs.uk) and PrescQIPP lipid modification e-learning (*registration required*)

Primary Prevention: Medicines Optimisation for Lipid Management in Primary Care

Please note: **Lifestyle change and dietary measures** are key to CVD event reduction alongside medicines optimisation (*see page 8*)

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, blood pressure (BP), weight, 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 if lipid profile may indicate FH (*see page 14*) and also manage secondary causes of high triglycerides (*see page 17*)

Patients with the following conditions are high CVD risk and require consideration for a high intensity statin (HIS) regardless of QRisk scoring: familial hypercholesterolaemia (FH)- *see page 14*, type 1 diabetes mellitus (T1DM), chronic kidney disease eGFR <60ml/min/1,73m2 (CKD) and/or albuminuria**. Offer** HIS to patients with **Type 1 DM** and **age >40 years** or patients with Type 1 **DM >10 years** or **nephropathy** or with **other CVD risk factors** NICECG181

Offer atorvastatin 20mg to patients with Type 2 DM with CV risk ≥ 10% and to all patients with CKD

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, severe mental illness, medications that may cause dyslipidaemia (eg. antipsychotics, corticosteroids, immunosuppressants), autoimmune disorders eg. systemic lupus erythematosus (SLE), impaired fasting glycaemia, significant hypertriglyceridaemia (*see pages 16-17*), recent change in risk factors eg change to smoking status, BP and lipid management

Consider options with shared decision making, education and lifestyle interventions to **modify CVD risk** *(see page 8)*

The decision whether to start statin therapy should be made after an informed discussion between the clinician and the person about the risks and benefits of statin treatment, taking into account additional factors such as potential benefits from lifestyle modifications, informed patient preference, comorbidities, polypharmacy, general frailty and life expectancy

For all patients consider the risk:benefit of therapy holistically and consider **deprescribing options** e.g. 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 management of BP and other co-morbidities. **Support** lifestyle interventions and medicines adherence.

If QRisk ≥10%: after addressing modifiable risk factors and following a shared decision: consider initiating or optimising statin therapy with a **moderate dose** of a **high intensity drug**: atorvastatin 20mg daily (alternative is rosuvastatin 10mg daily) -*see page 8 for HIS comparison table* -consider drug interactions that may affect dosing (see BNF)

After 3 months, has non-HDL cholesterol fallen by ≥ 40% from baseline? Check lipid profile and LFTs, adherence to medication, timing of dose, statin adverse effects/intolerance/hesitancy & diet/lifestyle interventions (*See page 6 for a review of patients not achieving targets in primary prevention)*

Yes

No

Step 1: Consider up-titration of statin to a maximum dose atorvastatin 80mg (alternative is rosuvastatin 20mg to 40mg)*- *see HIS table page 8 and consider dose-limitations in CKD (eGFR<30ml/min)*

Step 2: If intolerant to higher dose of statin, consider adding ezetimibe 10mg daily (SPC- check contra-indications) to maximal tolerated statin

Step 3: If intolerant to any statin, start ezetimibe 10mg daily and consider adding bempedoic acid 180mg daily ▼ (SPC) (*see statin intolerance pathway on page 7 for further information*)

After 3 months, has non-HDL cholesterol fallen by ≥ 40% from baseline? Check adherence to medication, adverse effects/intolerance/hesitancy and lifestyle interventions

Yes

No

Review annually for adherence to medications, diet and lifestyle, check required bloods as indicated eg lipids and LFTs (note: LFT repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity)

Refer to lipid clinic (*see page 10 for SEL contact details*)

***Please note** that for rosuvastatin 40mg specialist supervision is recommended when this dose is initiated (see SPC)

Secondary Prevention: Medicines optimisation for Lipid Management

1) **Check baseline bloods** (non-fasting full lipid profile, LFTs, HbA1c, thyroid and renal function)- also consider if lipid profile may indicate FH (*see page 14*) and manage secondary causes of high triglycerides as indicated (*see page 17*)

2) **Offer high dose high intensity statin** therapy with atorvastatin 40-80mg (alternative is rosuvastatin 20-40mg)* to adults with CVD: this includes acute coronary syndromes (ACS), angina, previous myocardial infarction (MI), revascularisation, stroke or transient ischaemic attack (TIA), symptomatic peripheral arterial disease (PAD) or abdominal aortic aneurysm (AAA)

3) **Support the self-management** (*see page 8*) of modifiable risk factors eg. smoking, diet, obesity, alcohol intake, physical activity, blood pressure and glycaemic control (HbA1c)

In primary care check: **Is patient on high dose, high intensity statin?** atorvastatin 40-80mg (alternative is rosuvastatin 20mg-40mg)*-consider *dose adjustments: eGFR<30ml/min, drug interactions, intolerance*

See page 6 for a review of patients with CVD not prescribed a statin in primary care

Yes

Has non-HDL-C reduced by 40% or more from baseline at 3 months? NICE (if no baseline value: consider a target of non-HDL-C < 2.5mmol/L or LDL-C <1.8mmol/L: JBS)

Check non-fasting full lipid profile (TC, TG, HDL, LDL-C); LFTs

Discuss with patient statin choice and alternative lipid lowering options: reinforce lifestyle and dietary measures- check adherence to medication and lifestyle

(*for statin intolerance pathway see page 7*)

No

Consider adding Ezetimibe 10mg daily SPC- *see page 13* for a summary of lipid lowering options to discuss with your patient

After 3 months, check non-fasting full lipid profile (TC, TG, HDL, LDL-C); LFTs

If confirmed statin intolerance (*see page 7*): consider combined bempedoic acid ▼with ezetimibe therapy (*see page 7*) or inclisiran ▼ (*see page 12*)

Yes

Has non-HDL-C reduced by 40% or more from baseline at 3 months? (if no baseline value: consider a target non-HDL-C < 2.5mmol/L or LDL-C <1.8mmo/L)

No

Refer to lipid clinic (advice and guidance) to **consider injectable therapies** (after checking LDL-C) and/or to consider oral icosapent ethyl (after also checking fasting TG)

If LDL ≥ 2.6 mmol/L consider inclisiran ▼initiation in primary or secondary care (*see page 12*) following advice from a lipid specialist (see *inclisiran initiation checklist*)

Refer to lipid clinic if LDL-C >4mmol/L (or LDL-C >3.5mmol/L with recurrent CVD event or multivascular disease) to **consider alirocumab or evolocumab (PCSK9i mAB)** *see page 9: PCSK9i mAB pathway*

If a patient with CVD, is adherent to current statin therapy, and has fasting TG ≥ 1.7mmol/L & LDL-C between 1.0 and ≤ 2.6mmol/L consider adding **icosapent ethyl**▼(*see pages 16-17*) to reduce CV risk

Review annually for adherence to medications, support for diet and lifestyle measures, and check required bloods as indicated e.g. lipid profile (to assess adherence and treatment targets), LFTs (especially after the first 12 months and then as clinically indicated e.g. hepatotoxicity)

***Please note** that for rosuvastatin 40mg specialist supervision is recommended when this dose is initiated (see SPC)

Optimising lipid management for patients in primary care: Supporting a review of priority cohorts in secondary and primary prevention of CVD

EMIS/UCLP (*see page 3*) search to identify

Secondary prevention: Patients with a CVD history and not currently prescribed a statin

- Review clinical information and full lipid profile results- recheck lipid profile and BP measurements if not from within the last year
- Discuss with the patient their reasons for not being prescribed a statin:

1. Non-adherence eg stopped after a period of time
2. Statin intolerance- has tried 2/3 different statins with adverse outcomes- consider alternative options/rechallenges (*see statin intolerance pathway page 7*)
3. Statin hesitancy- patient is reluctant to be prescribed a statin following discussions of risk: benefit- see decision making table *page 8*
4. Statin contra-indication- interacting medications, co-morbidities, frailty- document clearly decision made with patient and coding in medical notes
5. Statin refusal- despite best efforts and risk:benefit discussion- document clearly decision made with patient and coding in medical notes
6. Document reason using SNOMED code and/or restart HIS prescription- refer to community pharmacy for adherence support and schedule a follow up within 3 months

- Consider lifestyle/behavioural interventions

Potential Outcomes:

1. Prescribe atorvastatin 80mg daily or rosuvastatin 20mg daily.: Reduce dose according to renal function/drug interactions
2. Follow statin intolerance pathway consider ezetimibe and/or bempedoic acid (*see page 7*)
3. Refer to lipid specialist for further advice if statin intolerance (>2 statins)
4. Schedule a follow up with practice pharmacist or community pharmacist to support adherence
5. Refer to social prescriber as indicated to support lifestyle interventions
6. Documentation of statin contra-indication or refusal and alternative management strategies considered

Primary prevention: Patients with high CVD risk on sub-optimal intensity statin and/or not reaching lipid management targets

- Review clinical information, full lipid profile and liver function test results- recheck lipid profile and BP measurements if not from within the last year:

1. Calculate up to date Qrisk2 or QRisk3 score- focus review on scores >20% and/or high CV risk conditions such as FH, T1DM or CKD
2. Initiate or optimise HIS therapy (atorvastatin or rosuvastatin) *see page 4*
3. Add in ezetimibe and escalate therapy *see page 4* if non-HDL has not reduced by 40% from baseline or non-HDL >2.5 mmol/L after 3 months of maximum tolerated HIS therapy
4. Document statin intolerance/hesitancy/contra-indications (*as box above*)
5. Refer to lipid clinic or advice and guidance (A&G) as indicated

Potential outcomes:

1. Escalation of lipid management therapy eg. maximum tolerated HIS dosing and/or ezetimibe
2. Review therapy in 3 months: Titrate medication to achieve 40% reduction on non-HDL-C or <2.5mmol/L
3. Review and support adherence to medication, diet and lifestyle interventions
4. Refer to lipid clinic for support if not achieving targets (A&G for consideration of injectable therapies)

Statin intolerance pathway and alternative options for lipid management

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 (see AAC pathway)

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 (HIS), aim to treat with a maximum tolerated dose of a statin, but if symptoms persist consider alternative options/lipid clinic referral (*see below*)

For **Statin Related Muscle** (SRM) **symptoms:** symmetrical pain/weakness in large proximal muscle groups, worsened by exercise.
Measure creatine kinase (CK): if > 4x and <10x ULN with intolerable symptoms: stop statin for 4 to 6 weeks*

If CK normalises and symptoms have resolved for at least 2 weeks, then rechallenge: Offer a low/moderate dose of HIS eg atorvastatin 10 to 20mg daily or rosuvastatin 5 to 10mg daily.
Please note: Non-standard dosing may be prescribed by specialist clinics eg 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)
2) Add in ezetimibe 10mg daily (SPC)- review adherence/tolerance and full lipid profile in 3 months

If tolerating ezetimibe but not achieving lipid lowering targets: consider inclisiran▼(*page 12*) following specialist advice if for secondary prevention or consider initiating bempedoic acid 180mg daily▼ (SPC) in line with the following recommendations:

Bempedoic acid initiation: This is green on the SEL joint formulary and may be started in primary or secondary care settings:

1. Check baseline eGFR (do not start if eGFR <30ml/min)
2. Check baseline LFTs and uric acid (do not start in severe hepatic impairment eg. Child-Pugh C or active gout)
3. Check baseline FBC (particularly haemoglobin- Hb level)
4. Consider drug interactions eg simvastatin (BNF) and contra-indications (SPC)
5. Prescribe with ezetimibe 10mg. Where possible prescribe the combined bempedoic acid/ezetimibe formulation as this may support patient adherence and is more cost effective.
6. Communicate to primary care/record in patient record: baseline information at initiation and schedule follow up

Patient information: Report any unexplained muscle pain, tenderness or weakness. Report any gout symptoms (usually within the first month of therapy)

Bempedoic acid monitoring in primary care within the first 3 months and annually:

1. Continue prescribing if well tolerated and patient is adherent to therapy
2. Check LFTs- discontinue treatment if AST/ALT ≥3x ULN
3. Monitor for hyperuricaemia with gout symptoms- if present, discontinue bempedoic acid
4. Check FBC, stop if Hb decrease by ≥20g/L from baseline or < lower limit of normal (LLN), investigate other possible causes/refer to appropriate specialist
5. Monitor for myopathy symptoms- if present check creatine kinase (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 information: Report any unexplained muscle pain, tenderness or weakness.
Please note: some patients are intolerant to both statin and ezetimibe and may be recommended bempedoic acid monotherapy by the specialist (amber 1)

***For muscular symptoms:** check **CK: if >50x ULN** stop statin and consider rhabdomyolysis, **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.

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, following 3 months and within 1 year of statin therapy.

Shared decision making concerning lifestyle and statins

Lifestyle interventions: There are many resources to support self-management eg Heart UK and British Heart Foundation, national support groups and local social prescribing options. Support the patient to review their diet (NHS Eat Well) exercise, smoking cessation, alcohol intake 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)*

	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

	Approximate reduction in LDL-C					
Choice of statin or oral lipid lowering therapy/ daily dose	5mg	10mg	20mg	40mg	80mg	NB. High intensity statins (HIS) reduce LDL-C >40% (highlighted green) and are more effective at preventing cardiovascular events than low/medium intensity statins NICE/AAC recommends atorvastatin and rosuvastatin as HIS *simvastatin 80mg is not recommended due to muscle toxicity risk
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%*					*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

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

PCSK9 Inhibitors (monoclonal antibodies-mABs)

If still not achieving targets, or following confirmed statin intolerance, **refer to lipid clinic** *(see page 10 for contact details)* for consideration of initiation of PCSK9i (mAB).

NICE eligibility criteria for alirocumab or evolocumab are established CVD or familial hypercholesterolaemia:

NICE TA eligibility criteria for PCSK9i (mAB)	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 mAB (red formulary status, hospital only medications) either: *(NB. there is no first line PCSK9i mAB in SEL)*

- **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) **or**
- **EVOLOCUMAB** 140mg SC injection every 2 weeks or 420mg once monthly (for FH, after 12 weeks of treatment, the dose may be uptitrated to 420mg every 2 weeks if a clinically meaningful response is not achieved)

Continue existing oral lipid lowering therapy and assess response within 3 months of initiation.

For primary care: see *SEL Guide to reconciling hospital only medicines in primary care*

LDL-C reduction >30%

CONTINUE therapy and ongoing review by lipid clinic

(*hospital only prescribing: PCSK9i mAB are RED on formulary*)

Intolerance/adverse event

DISCONTINUE therapy and consider alternative lipid lowering options including switch of PCSK9i mAB

Lipid clinic to communicate action plan to primary care

LDL-C reduction <30%:

Check adherence and injection technique

Consider uptitration of dose/alternative PCSK9i mAB or consider discontinuation and alternative lipid lowering options (*see page 13*) if inadequate response persists with PCSK9i mAB

Lipid clinic to communicate lipid management plan to primary care

Please note that inclisiran also inhibits PCSK9 production by interfering with RNA, and reduces LDL- cholesterol levels, but has differing NICE eligibility criteria and may be administered in primary and secondary care (*see page 12*)

SEL Lipid Specialist Services and Contact Details

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:		
SEL Lipid Clinic	**Lipidologist for referrals**	**Contact Details**
GSTT	Prof AS Wierzbicki/Prof MA Crook	via Choose & Book or gst-tr.diabetesandendocrine@nhs.net
KCH	Dr Nandini Rao	via Choose & Book or to book an appointment/query re appointment/blood test request forms Tel: 02032994181 or email: Laura.Gonzalez@nhs.net
PRUH	Dr Nandini Rao	via eRS or kch-tr.br-referrals@nhs.net
LGT	Prof MA Crook	via Choose & Book or tlh-tr.LewishamReferrals@nhs.net or endocrinology at QEH: lipidology clinics at the Bromley diabetes centre, Outpatients QEH: Tel 02088364969
Community	Lambeth, Southwark and Bexley boroughs	Forms on DXS and/or email: gst-tr.KHPCommunityCVD@nhs.net

The aim of hospital and community clinics is to focus on patients with primary hyperlipidaemia, before referral please exclude:

- 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), excess alcohol intake and fatty liver (may require referral to gastro if FIB-4 score indicates)- *see page 17*
- For suspected familial hypercholesterolaemia exclude secondary causes and refer to the hospital based lipid clinic not the community clinic- *see pages 14 & 15*

Recommended Criteria For Referral to Lipid Clinic (SEL Hospital and Community Settings)

Hospital lipid clinic	Referral Criteria	Community lipid service	Referral criteria (Lambeth, Southwark and Bexley boroughs)
1. Severe hypercholesterolaemia	Cholesterol >9.0 mmol/L (or non HDL-C > 7.5 mmol/L) regardless of existing heart disease / family history	**1. Statin intolerance**	Intolerance of 3 or more statins OR Severe adverse reaction to one statin AND not meeting target reductions in LDL-C/ non HDL-C on ezetimibe 10mg daily.
2. Suspected familial hypercholesterolaemia (FH)	Cholesterol >7.5 mmol/L and LDL-C >5.0 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	**2. Secondary prevention of CVD**	Unable to meet target reductions in LDL-C or non HDL-C despite maximal doses of statins + ezetimibe
3. Family screening	Cascade screening from identified patient with familial hypercholesterolaemia with a genetic diagnosis of FH	**3. Medicines adherence support**	Persistent non-adherence to drug therapies despite best efforts of the GP practice
4. 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	Please note the community clinic will also undertake follow up of specific patients reviewed in secondary care specialist lipids services and discharged with a management plan suitable for primary care. *Currently community clinics run by GSTT are available in Lambeth, Southwark and Bexley boroughs, with community CVD hub pilots from 2023 in Bexley, Greenwich and Lewisham to support the lipid management pathway as part of the Protect your Heart lipid transformation project* *See page 10* for lipid clinic contact details	
5. 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		
6. Secondary prevention of CVD	Unable to meet target reductions in LDL-C or non HDL-C despite maximal doses of statins + ezetimibe		

SEL Process for Inclisiran Initiation (including Switching Patients from PCSK9i mAB to Inclisiran)

Indication for inclisiran (assessed by lipid specialist): Does the patient have?

1. CVD history e.g. ACS, coronary/arterial revascularisation, CHD, ischaemic stroke or peripheral arterial disease (PAD)
2. LDL levels >2.6mmol/L- baseline check (prior to any PCSK9i therapy)
3. Maximally tolerated statins and/or ezetimibe and dietary measures but not achieving treatment targets in secondary prevention (and require additional therapy)

AND/OR

4. Secondary prevention with a contra-indication or intolerance/poor adherence to PCSK9i mAB* (alirocumab or evolocumab), statins and/or ezetimibe

AND

5. No cautions-such as: severe renal impairment (eg CrCl <30ml/min) or requiring haemodialysis (avoid 72 hours after inclisiran dosing), pregnancy and breast-feeding, severe liver impairment (Child-Pugh class C), child <18 years

No → Not suitable for inclisiran- HCD payment will not be possible as not in line with NICE criteria: IFR required: refer to medicines optimisation team or trust formulary pharmacist for additional support

*Patients requiring a switch from PCSK9i mAB to inclisiran will be identified and initiated by a lipid specialist according to the NICE TA criteria

Yes

Initiation visit: In SEL inclisiran is amber 1: initiation on the recommendation of a specialist

1. Inclisiran Initiation checklist completed (and discussed with lipid specialist) and a risk:benefit discussion with the patient has been documented (see Novartis PIL for Leqvio ®):
2. In secondary care: BlueTeq form completed for reimbursement of costs (PAS discounted price per patient registered); in primary care: inclisiran supplies are ordered from AAH to be delivered to the practice OR prescribed on FP10 and collected from community pharmacy for administration at the practice (reimbursement claimed via FP34D submission to NHS BSA)
3. Check full lipid profile, liver and renal function
4. Administration appointment planned with follow ups scheduled at 3 months and then every 6 months at secondary care/community lipid clinic or primary care *(check local pathway)*
5. Dose given by HCP with competence to administer inclisiran: 284mg subcutaneous (SC) injection into abdomen (upper arm or thigh) see Leqvio®inclisiran administration how to guide
6. If started in secondary care: Clinic letter sent to primary care to inform of new regime and follow up requirements. In primary care: schedule follow up appointments as below and/or with support of acute lipid clinic (*until community pathway is established*)

3 month follow up visit :

1. Check for adverse effects and intolerance eg injection site reactions- report all ADRs to MHRA (yellow card)
2. Lipid profile repeated
3. Repeat dose administered 284mg SC (following clinical assessment)

If patient DNA or lost to follow up → If this visit is delayed by <3months, administer inclisiran and continue dosing schedule
If the dose is missed by ≥3 months, start a new dosing schedule- baseline, 3 months and then 6 monthly

6 monthly follow up visits:

1. Check for adverse effects and intolerance eg injection site reactions- report all ADRs to MHRA (yellow card)
2. Lipid profile repeated *(check liver function tests if indicated/adverse effects)*
3. Repeat dose administered 284mg SC (following clinical assessment) and then every 6 months
4. Each year check: adherence to all medications, diet and lifestyle interventions, bloods: full lipid profile, liver and renal profile

If delay to follow up → If this visit is delayed by <3months, administer inclisiran and continue dosing schedule
If the dose is missed by ≥3 months, start a new dosing schedule- baseline, 3 months and then 6 monthly

If LDL lowering is not to target → If LDL remains above 2.6mmol/L despite 9 to 12 months of inclisiran-review therapy and lifestyle interventions- seek advice and guidance from lipid specialist

Summary of Lipid Lowering Options and CV risk reduction

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- CLEAR outcomes)	Awaited
Inclisiran (PCSK9i)	Secondary prevention if LDL >2.6mmol/L, statin intolerance	SC injection twice a year	52%	Awaited	Awaited
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

Familial Hypercholesterolaemia (FH) Pathway

In primary care case find age <30 years:

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

In primary care case find age ≥30 years:

TC >9.0mmol/L or LDL-C >6.4mmol/L or non-HDL-C >7.5mmol/L

In primary care check bloods: repeat non-fasting 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 (refer if indicated- *see pages 16 & 17*) and aim to reduce non-HDL-C by 40% (*see primary and secondary prevention pathways: pages 4 & 5*). **Ensure appropriate SNOMED coding in primary care record:** hypertriglyceridemia and/or hypercholesterolaemia, not FH.

Primary care check:

1. Family history: 1st degree relative MI <60 years old, 2nd degree relative MI <50 years old and/or family history of raised cholesterol >7.5mmol/L
2. Tendon xanthomata, xanthelasma or corneal arcus

If either are positive refer to lipid clinic for DNA testing for monogenic FH (Simon Broome criteria)- exclude any secondary causes before referral

If not confirmed FH

If confirmed FH*: aim to reduce LDL by >50%, **lipid clinic will initiate/recommend options:**

1. High intensity statin (atorvastatin or rosuvastatin- maximum tolerated doses- *see HIS table on page 7*)
2. Add in ezetimibe 10mg daily
3. Add in bempedoic acid 180mg daily (to ezetimibe) if statin intolerance (*see page 7*) or inclisiran if secondary prevention (*see page 12*) or alirocumab or evolocumab (*see PCSK9i mAB pathway on page 9*) if not achieving targets

Specialist service for monogenic FH: genetic counselling and DNA test for FH mutation (this is available at all secondary care lipid clinics in SEL) and cascade testing for family members if indicated (available at GSTT)

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

Familial Hypercholesterolaemia (FH) review in primary care: Supporting identification, diagnosis, management and coding

Priority 1: Review of patients coded as FH

EMIS/UCLP search to identify (*see page 3*)

Priority 2: Identification of FH- age and lipid profile:

<30 years: TC >7.5 or LDL-C >4.9 or non-HDL-C >6.0 (mmol/L)

≥30 years: TC >9.0 or LDL-C >6.4 or non-HDL-C >7.5 (mmol/L)

Review medical records for patients coded as FH (*see SNOMED codes listed below*). Consider the following:

1. Has the patient had FH confirmed with a genetic test by secondary care specialist lipid clinic? If yes go to Q2, if no go to Q3
2. If FH is confirmed: Has the patient been reviewed within the last 5 years by the lipid specialist? If not consider advice and guidance (A&G) from secondary care lipid clinic as required to ensure achieving lipid management targets and CV risk reduction in FH

Has the patient with FH received cascade testing for family members? Lipid clinic may refer to genomics nurse clinic (*available at GSTT from 2023*)

3. If FH is not confirmed: amend coding (highlight code and replace with new code eg hypercholesterolaemia)- EMIS note that coding has changed and let patient know by letter/text message if an update to therapy or consultation is required if not during a F2F review: *use SNOMED codes listed in box below and review all of below:*

- Review lipid profile (high TC or LDL or non-HDL levels according to age may indicate FH- see priority 2 cohort below)
- Review triglyceride (TG) level (if >2.3mmol/L unlikely FH but need to investigate cause eg fatty liver and code for hypertriglyceridaemia)
- Review Simon Broome criteria (eg. family history of MI <60 years, tendon xanthomata)
- Exclude secondary causes: eg. alcohol >40 units/week, ALT >40, TG >5, HbA1c >7%, TSH >15, CKD 3, liver failure, non-alcoholic fatty liver disease, and manage as appropriate (eg fatty liver guidance)
- Consider CV risk and CVD history: ensure Qrisk score 2 or 3 is up to date (if primary prevention): check BP, weight, lifestyle and blood tests: manage with appropriate interventions as indicated (eg. if QRisk >10% in primary prevention start HI statin- *see page 4*)
- Refer to lipid clinic (if lipid profile and Simon Broome criteria indicate FH but NOT if TG levels and secondary causes exclude FH)

Review medical records and invite appropriate patients for a face- to- face screening appointment:

1. Repeat full lipid profile (TC, TG, HDL-C, LDL-C)
2. Decide with the patient to start HIS or escalate lipid management therapy as appropriate: *See pages 4 and 5*
3. Consider clinical signs of FH and family history: Simon Broome criteria
4. Rule out and manage secondary causes: e.g. high alcohol intake, liver impairment, high triglycerides, uncontrolled diabetes, hyperthyroidism, renal impairment and liver failure; also consider in females if TC increase is due to menopause or in pregnancy or breastfeeding. Add exception note to GP record alongside hypercholesterolaemia or "possible FH" code to show a primary care review has occurred.
5. Refer to lipid clinic for genetic diagnosis as indicated- code as "possible" or "probable FH" in primary care record until clinic review
6. Signpost to patient information for FH and lifestyle interventions: Familial hypercholesterolaemia| British Heart Foundation (bhf.org.uk); familial-hypercholesterolaemia.pdf (heartuk.org.uk)

Potential Outcomes:

1. Use FH referral form to refer to specialist lipid clinic in secondary care as indicated: for diagnosis or management support

2. Ensure coding is correct for each patient- adjust as required

3. Consider lifestyle and medication interventions and schedule follow up

Suggested SNOMED Coding:
Single gene FH: Familial hypercholesterolemia (disorder) SCTID: 398036000
Family history of familial hypercholesterolemia (situation) SCTID: 443454007
Other high cholesterol coding: *Hypercholesterolemia (disorder)* SCTID: 13644009
Family history: Hypercholesterolemia (situation) SCTID: 160314003

Guidance for the management of hypertriglyceridaemia

Triglycerides (TG) >2 to <4.5 mmol/L

If CVD risk <10%

Manage secondary causes of hyperlipidaemia and CV risk with lifestyle interventions (*see page 17*)

If CVD risk ≥10%

Manage secondary causes of hyperlipidaemia and CV risk with lifestyle PLUS consider a high intensity (HIS) statin for primary prevention (see *page 4*)

TG ≥4.5mmol/L to <10mmol/L

Repeat fasting lipid profile (after 5 days but within 2 weeks)

Repeat QRisk and optimise CV risk factor management

If non-HDL > 7.5mmol/L refer to lipid clinic

If Qrisk <10% consider a fibrate* (*see page 17)

If Qrisk ≥10% or if CVD history consider HIS (*see pages 4&5*)

If inadequate response

TG ≥10 to <20mmol/L

Repeat fasting lipid profile (after 5 days but within 2 weeks)

Review and manage potential secondary causes of hypertriglyceridaemia (*page 17*)

If TG remains ≥10mmol/L

Refer to lipid specialist

TG ≥20mmol/L

Urgent referral to lipid specialist as high risk of pancreatitis

Review and manage secondary causes e.g. excess alcohol and poor glucose control

Refer to lipid specialist

In selected patients (e.g.pancreatitis risk) omega 3 fatty acids may be initiated by lipid specialists for the control of triglycerides

In patients with a CVD history, fasting TG>1.7mmol/L (or non-fasting TG >2.1mmol/L) and LDL-C 1.04 to 2.6mmol/L, cardiovascular, diabetes and lipid specialists may consider adding icosapent ethyl ▼ to HIS therapy (*see page 17*) NICE TA

Management of triglycerides

SNOMED code: hypertriglyceridemia 302870006

- In all cases address possible secondary causes and appropriate lifestyle interventions:
  - Excessive alcohol intake (e.g. >40 units/week)
  - Poorly controlled/new diabetes (e.g. HbA1c >7%)
  - TG –raising medication (e.g. steroids)
  - Hypothyroidism (e.g. TSH >15)
  - Non-alcoholic fatty liver (see guidance)
    - assess risk of advanced liver fibrosis: Fibrosis (FIB) 4 score (refer to hepatology)
  - Acute/chronic liver disease (e.g. ALT >40)
  - Renal disease (e.g. CKD 3)
  - Obesity
  - Smoking
- Ensure that these have been reviewed before referral to lipid clinic

*Fibrate therapy: such as fenofibrate 160mg daily SPC (if contra-indicated or not tolerated seek specialist advice)

- recheck lipid levels within 3 months of initiation, aiming for TG <4.5mmol/L

Monitor: Serum creatinine (Cr) at baseline, within 3 months and annually (or as clinically indicated)
Liver function tests e.g. ALT/AST every 3 months for first year of therapy and then as indicated
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

▼Icosapent ethyl therapy:

NICE TA recommends for patients with CVD (secondary prevention) and LDL-C > 1.0mmol/L and ≤ 2.6mmol/L with fasting TG >1.7mmol/L **in combination with statin therapy** *(see page 5 for lipid optimisation pathway in secondary prevention)*

- In SEL this is amber 2- initiation by and first prescription from a cardiovascular, diabetes or lipid specialist followed by primary care prescribing according to NICE specifications above
- Dosage: 2 x 998mg capsules twice a day taken with food
- Cautions (SPC): patients with fish/shellfish allergies, hepatic impairment (check ALT/AST before starting and periodically as clinically indicated), 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), history of gout
- Contra-indicated: in pregnancy and breastfeeding, hypersensitivity to soya or peanuts
- Adverse effects: see SPC and report any adverse effects to MHRA ▼
- Patient information: awareness of palpitations and bleeding risk- need to report; adherence support
- Adherence: 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. 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.

Glossary of terms

- Abbreviations used for lipid profiles:
  - 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
  - Calculating non-HDL-C =

total cholesterol- HDL cholesterol

- mAB: monoclonal antibody
- FH: familial hypercholesterolaemia
- ICS: integrated care system
- CV: cardiovascular
- CVD: cardiovascular disease
- LFTs: liver function tests
- DM: diabetes mellitus
- CKD: chronic kidney disease
- BP: blood pressure
- HIS: high intensity statin
- AST/ALT: aspartate aminotransferase/alanine transaminase
- TSH: thyroid stimulating hormone
- Cr: Creatinine
- CK: creatine kinase
- ECG: electrocardiogram
- AF: atrial fibrillation
- PCSK9i: Proprotein convertase subtilisin/kexin type 9 inhibitors
- SC: subcutaneous
- PAS: patient access scheme
- ACS: acute coronary syndrome
- CrCl: creatinine clearance
- HCD: high cost drug
- IFR: individual request for funding
- PIL: patient information leaflet
- ADR: adverse drug reaction
- BSA: Business Services Authority
- RNA: ribonucleic acid
- PAD: peripheral arterial disease
- AAH: Pharmaceutical distribution service

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