Lipid Management: Medicines Optimisation Pathways

South East London (SEL) Integrated Care System

September 2021

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

Approval date: September 2021 **Review date: September 2023 (or sooner if evidence or practice changes)**

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

Contents

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

Non-HDL-C = total cholesterol- HDL cholesterol

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 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.

Primary Prevention: Medicines Optimisation for Lipid Management

Lifestyle change and dietary measures are key to CVD event reduction together with drug therapy

In primary care check: bloods (non-fasting 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 QRisk2 score using EMIS template (www.qrisk.org)

Please note **QRisk2 does not apply in the following conditions**: familial hypercholesterolaemia (FH), type 1 diabetes mellitus (T1DM)- *may be applied to QRisk3 calculations*, chronic kidney disease CKD (*QRisk3 has updated to eGFR <30ml/min; NICE states eGFR <60ml/min*) and/or albuminuria- **these patients are high CVD risk and require consideration for a high intensity (HI) statin. Offer** HI statin to patients with **Type 1 DM** and **age >40 years** or **DM >10 years** or **nephropathy** or with **other CVD risk factors** *NICE[6]*

Consider additional CVD risk factors, if present, together with 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 page 9*), recent change in risk factors eg change to smoking status, BP and lipid management

Consider options with sh**ared** decision making (*see page 6*), education and lifestyle interventions to **modify CVD risk.**
For all patients consider the risk:benefit of therapy holistically: for example in patients aged ≥ 85years consider frailty, life expectancy and co-morbidities

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 6 for high intensity statin comparison table* -consider drug interactions that may affect dosing (see BNF)

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

Yes

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 6*

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

Step 3 in primary care with secondary care support: If intolerant to any statin, start ezetimibe 10mg daily, **and refer to lipid clinic** to consider adding bempedoic acid 180mg daily ▼ (SPC) (*see statin intolerance pathway on page 5 for further information*)

Yes

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

No

Review annually for adherence to medications, diet and lifestyle, check required bloods eg lipids. Refer for support as required from specialist teams.

Refer to lipid clinic (*see page 7 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 lipid profile, LFTs, HbA1c, thyroid and renal function)

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 6*) 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*

Yes

Has non-HDL-C reduced by 40% or more from baseline at 3 months? NICE[6] (if no baseline value: consider a target of non-HDL-C < 2.5mmol/L or LDL-C <2.0mmo/L: JBS)

No

Discuss with patient statin choice: reinforce lifestyle and dietary measures-check adherence to medication and lifestyle (*for statin intolerance pathway see page 5)*
- After 3 months check non-fasting lipid profile (TC, TG, HDL, LDL-C); LFTs

Yes

Has non-HDL-C reduced by 40% or more from baseline at 3 months? NICE[6] (if no baseline value: consider a target of non-HDL-C < 2.5mmol/L or LDL-C <2.0mmol/L).
Check adherence to statin and lifestyle measures (*for statin intolerance see page 5*)

No

Consider adding Ezetimibe 10mg daily SPC

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

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 <2.0mmo/L)

No

Following a review of adherence/adverse effects/intolerance/hesitancy and lifestyle interventions. **Refer to lipid clinic**

If LDL-C >4mmol/L (or LDL-C >3.5mmol/L with recurrent CVD event or multivascular disease) lipid clinic will consider PCSK9i (*see page 7: PCSK9i pathway and contact details for SEL lipid clinics*)

If statin intolerance and/or not achieving targets, lipid clinic will consider addition of bempedoic acid ▼to ezetimibe therapy (*see page 5*)

Review annually for adherence to medications, support for diet and lifestyle measures, and check required bloods eg lipid profile, LFTs if indicated

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

Statin intolerance pathway/options if not achieving lipid lowering targets

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/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 HI statin 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: 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 lipid profile in 3 months

If tolerating ezetimibe but not achieving lipid lowering targets: **Refer to lipid clinic** to consider adding in bempedoic acid 180mg daily▼ (SPC)

Bempedoic acid initiation: This is amber 2 in SEL and will be undertaken by specialist lipid services:
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
6. Communicate to primary care: baseline information at initiation and recommendations for follow up in primary and/or secondary care (*lipid clinics may also have capacity to schedule a review at 3 to 6 months*)

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

Bempedoic acid monitoring in primary care within the first 3 months and annually:
1. Check LFTs- discontinue treatment if AST/ALT ≥3x ULN
2. Monitor for hyperuricaemia with gout symptoms- if present, discontinue bempedoic acid
3. 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
4. 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.

***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.5

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

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, 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					NB. High intensity (HI) statins 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 HI statins *simvastatin 80mg is not recommended due to muscle toxicity risk
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%*					*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)

Lipid Clinic Referral and PCSK9 Inhibitors

If still not achieving targets, or following confirmed statin intolerance, **refer to lipid clinic** for consideration of initiation of PCSK9i. *NICE eligibility criteria for PCSK9i 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 (red hospital only medications), either: (*NB. there is no first line PCSK9i 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 review 6 monthly by lipid clinic (*hospital only prescribing: PCSK9i are RED on formulary*)

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 PCSK9i or consider discontinuation and alternative lipid lowering options if inadequate response persists with PCSK9i. 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:

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 Choose &Book 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	Prof AS Wierzbicki for Lambeth, Southwark and Bexley boroughs	Forms on DXS and/or email: gst-tr.KHPCommunityCVD@nhs.net

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

Unlikely FH: Investigate raised triglycerides-TG (refer if indicated) and aim to reduce non-HDL-C by 40% (*see primary and secondary prevention pathways: pages 3 and 4*). **Ensure appropriate SNOMED coding in primary care record:** hypertriglyceridemia and/or hypercholesterolaemia, not FH.

If TG ≤ 2.3mmol/L

Primary care check:

1. Family history: 1st degree relative MI <60 years old, 2nd degree relative MI <50 years old
2. Tendon xanthomata

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

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 high intensity statin table on page 6*)
2. Add in ezetimibe 10mg daily
3. Add in bempedoic acid 180mg daily (to ezetimibe) if not reaching target/statin intolerance
4. Refer to lipid clinic for PCSK9i (*see pathway on page 7*)

Specialist service for monogenic FH: genetic counselling and DNA test for FH mutation and cascade testing for family members if indicated. This is available at all lipid clinics in SEL.

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

Management of triglycerides (TG)

SNOMED code: hypertriglyceridemia 302870006

Triglyceride concentration	Action
In all cases: Review secondary causes	Exclude secondary causes of high triglycerides such as - Excess alcohol intake - Poorly controlled/new diabetes - TG-raising medication (eg. high dose steroids)
Greater than 20mmol/L	• Refer to lipid clinic for urgent specialist review due to the risk of acute pancreatitis • In selected patients 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
10 to 20 mmol/L	Repeat TG with a fasting test (5 to 14 days after first test) and review potential secondary causes of hyperlipidaemia • Seek specialist lipid clinic advice if TG remains >10mmol/litre as risk of acute pancreatitis
4.5 to 9.9 mmol/L	If non-fasting TG >4.5mmol/L repeat with a fasting TG. Optimise management of other CVD risk factors (check Qrisk) • Seek specialist advice if non-HDL > 7.5mmol/litre. IF CVD risk (Qrisk) <10% consider a fibrate such as fenofibrate 160mg daily SPC (if contra-indicated or not tolerated seek specialist advice)- recheck lipid levels within 3 months of initiation- aim for TG <4.5mmol/L- monitor renal function and liver function with fibrate prescriptions at 3 months & annually If CVD risk (Qrisk) ≥10% consider a HI statin for primary prevention (*see page 3*) • Refer to lipid specialists if inadequate responses to therapy
>2 to <4.5 mmol/L	If CVD risk (Qrisk) <10% address any lifestyle factors If CVD risk (Qrisk) >10% consider a HI statin for primary prevention (*see page 3*)

Recommended Criteria For Referral to Lipid Clinic

Hospital lipid clinic	Referral Criteria	Community lipid service	Referral criteria (Lambeth, Southwark and Bexley boroughs)
Severe hypercholesterolaemia	Cholesterol >9.0 mmol/L (or non HDL-C > 7.5 mmol/L) regardless of existing heart disease / family history	**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.
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	**Secondary prevention of CVD**	Unable to meet target reductions in LDL-C or non HDL-C despite maximal doses of statins + ezetimibe
Family screening	Cascade screening from identified patient with familial hypercholesterolaemia with a genetic diagnosis of FH	**Medicines adherence support**	Persistent non-adherence to drug therapies despite best efforts of the GP practice
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.* 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) and excess alcohol intake	
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 + ezetimibe		

References and supporting material

1) **UCLPartners April 2021** Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia: https://s31836.pcdn.co/wp-content/uploads/Lipids-and-FH-Framework_UCLPartners-LTCs-April-2021-v4.1.pdf
2) **NHSE/AAC April 2020:** Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/lipid-management-pathway-guidance.pdf
3) **NHSE/AAC June 2020:** statin intolerance pathway: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/09/statin-intolerance-pathway-03092020.pdf
4) **Lancet 2016**; 388:2532-61; R Collins et al; Interpreting the evidence for the efficacy and safety of statin therapy; https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)31357-5.pdf
5) **AHA Scientific Statement**: Statin safety and associated adverse events; Arteriosclerosis, thrombosis and vascular biology 2019;39:e38-e81: https://www.ahajournals.org/doi/10.1161/ATV.0000000000000073
6) **NICE CG181:** Cardiovascular disease: risk assessment and reduction, including lipid modification clinical guideline; 18 July 2014: https://www.nice.org.uk/guidance/cg181/resources/cg181-lipid-modification-update-patient-decision-aid2
7) **NICE CG71:** Familial hypercholesterolaemia: identification and management; August 2008, updated Oct 2019: https://www.nice.org.uk/guidance/cg71
8) **NICE TA694; Bempedoic acid with ezetimibe** for treating primary hypercholesterolaemia or mixed dyslipidaemia, Published: 28 April 2021: https://www.nice.org.uk/guidance/ta694
9) **NICE TA385; Ezetimibe** for treating primary heterozygous-familial and non-familial hypercholesterolaemia, Published: 24 February 2016**:** https://www.nice.org.uk/guidance/ta385
10) **NICETA394; Evolocumab** for treating primary hypercholesterolaemia and mixed dyslipidaemia, Published: 22 June 2016: https://www.nice.org.uk/guidance/ta394
11) **NICE TA393; Alirocumab** for treating primary hypercholesterolaemia and mixed dyslipidaemia, Published: 22 June 2016: https://www.nice.org.uk/guidance/ta393
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: https://pubmed.ncbi.nlm.nih.gov/31357887/