104FM.3 LIPID MODIFICATION FOR NON-FAMILIAL HYPERCHOLESTEROLAEMIA (FOR ADULTS)

CONTENTS

Key Priorities for Implementation:

1. Clinicians should prioritise secondary prevention patients and those primary prevention patients at higher risk.
2. Before offering statin treatment, discuss lifestyle advice including smoking cessation, diet and weight loss, physical activity and alcohol reduction (see Appendix 1: **Lifestyle Advice** for more details). Optimise the management of other cardiovascular disease (CVD) risk factors. All patients offered statin therapy should have a full discussion on benefits versus risks and this should be documented in the notes.
3. Offer atorvastatin 80 mg for secondary prevention. Exceptions to this include:
   - Chronic kidney disease (CKD) - starting dose 20 mg, titrating up according to response (see Algorithm 2)
   - Active liver disease; persistent transaminase >3 times upper limit of normal (ULN) (see Table 3, Statin Monitoring and Follow-Up)
   - Pregnancy and breastfeeding
   - Haemorrhagic stroke or strokes not due to atherosclerosis – appropriateness of using high dose statin regimens should be decided on an individual patient basis following advice from stroke specialists.
4. Use QRISK assessment tool to assess the CVD risk:
   - For primary prevention of CVD in people ≤84 years (unless CKD or other high risk group – see Algorithm 1)
   - In people with type 2 diabetes

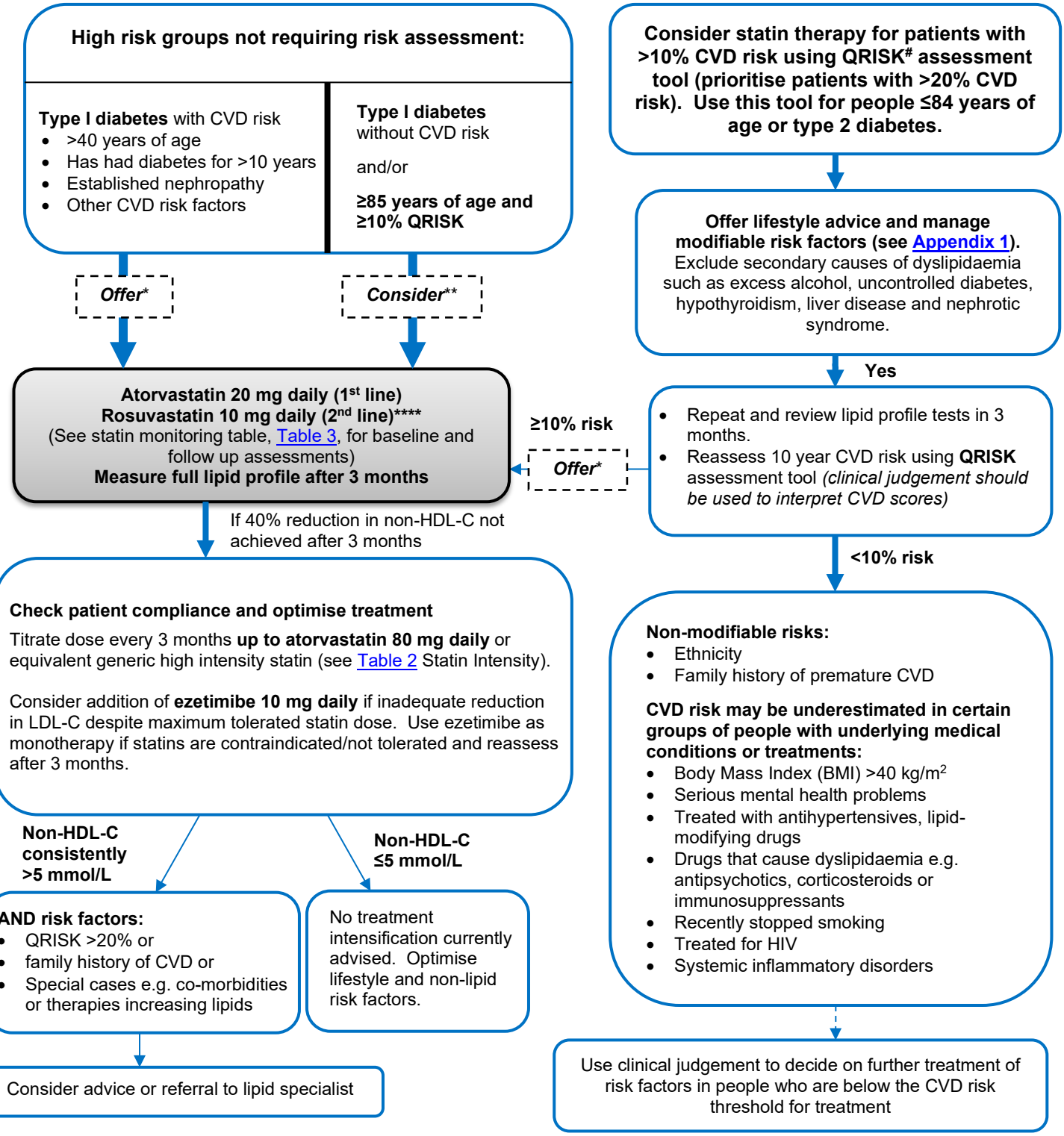
   QRISK3 is the current version of the QRISK calculator (http://qrisk.org/three)
5. **Do not use QRISK** for the following patient groups as it may underestimate risk:
   - Age over 84 years
   - Established cardiovascular disease
   - In people with type 1 diabetes – National Institute for Health and Care Excellence (NICE) recommends considering statin (see Algorithm 1)
   - Familial hypercholesterolaemia (FH) or risk of inherited dyslipidaemia
   - Glomerular filtration rate (GFR) <60 mL/min, estimated GFR (eGFR) <60 mL/min/1.73 m^2 and/or albuminuria

6. For primary prevention of CVD, it is recommended to use a **systematic strategy** to identify people at high risk (e.g. the NHS Health Check programme). NICE defines high risk as an estimated CVD risk of 10% or more over 10 years. Bucks advise a step-wise approach, giving priority to patients with 20% or greater CVD 10 year risk.
7. Measure a full lipid profile before starting lipid modification therapy. A fasting sample is not required.
   - Full lipid profile includes total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), non-HDL-C, triglyceride concentrations and a calculated low-density lipoprotein cholesterol (LDL-C).
8. Measure total cholesterol, HDL-C and non-HDL-C in all people who have been started on a high intensity statin treatment at 3 months and aim for greater than 40% reduction in non-HDL-C.
9. NICE have produced a series of patient decision aids (PDAs) to enable patients to assess the risks and benefits of commencing statins.
10. For patients with total cholesterol >7.5 mmol/L and family history of premature coronary heart disease (CHD) consider FH and manage in accordance with NICE CG71 Familial Hypercholesterolaemia.

Algorithm 1: Primary Prevention for New Patients WITHOUT Chronic Kidney Disease (CKD)

For patients with CKD see Algorithm 2: Secondary Prevention.

For familial hypercholesterolemia see NICE CG71 Familial Hypercholesterolaemia

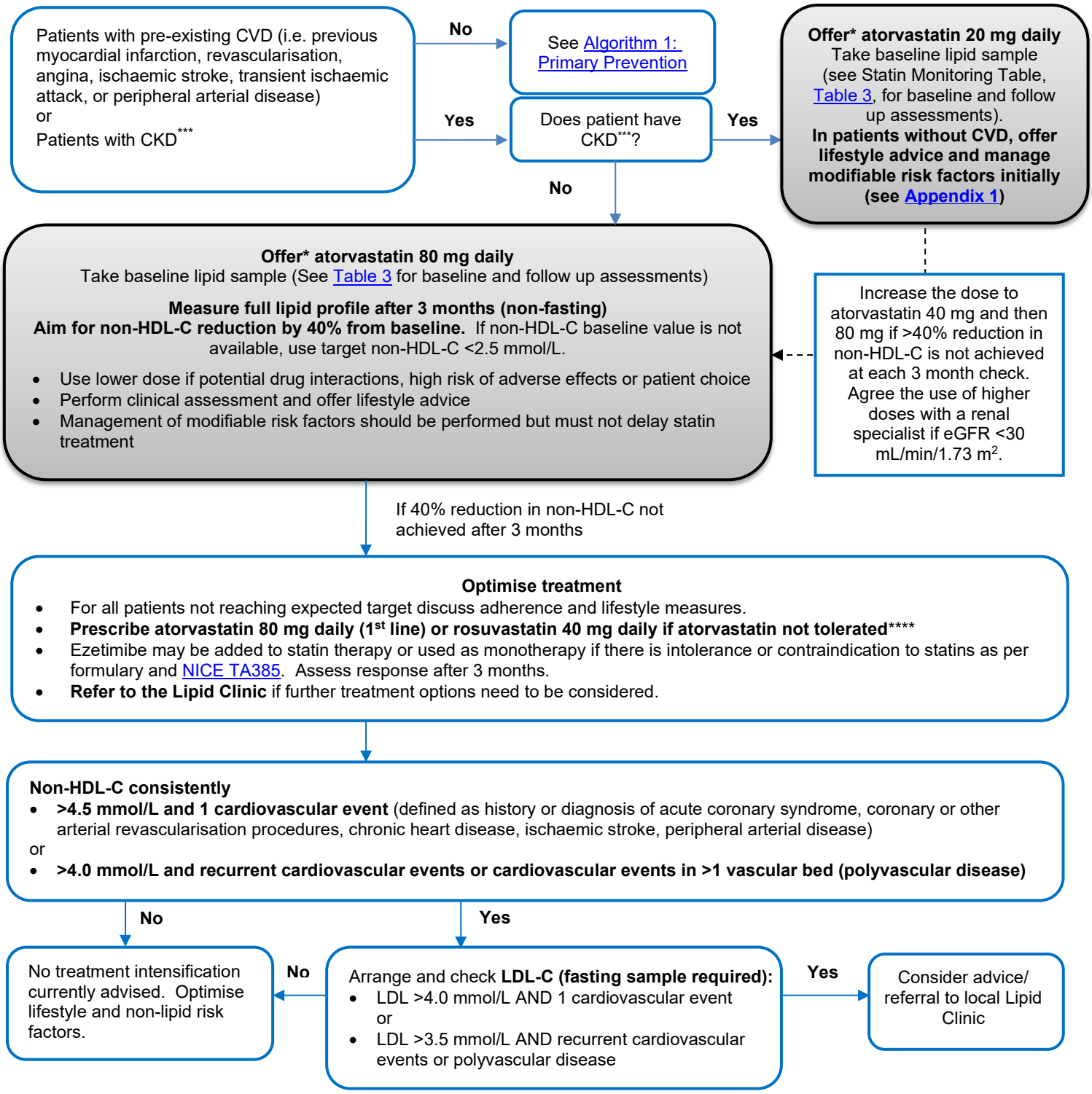


QRISK is not yet integrated onto GP clinical systems.

NICE define
*__Offer__ as an intervention which will do more good than harm and be cost effective
**__Consider__ as an intervention which will do more good than harm for most patients and be cost effective, but other options may be similarly cost effective

****For rosuvastatin prescribing, please see additional considerations on dosing below

Algorithm 2: Secondary Prevention for NEW Patients including those with Chronic Kidney Disease (CKD) and Primary Prevention for NEW Patients with CKD



NICE define

*** Chronic kidney disease (CKD) is defined as GFR <60 mL/min and/or albuminuria (G3a, A2)[6]. Bucks advise prioritising patients with GFR <45 mL/min (G3b, A2). See **NICE CG182**.

****For rosuvastatin prescribing, please see additional considerations on dosing below

Existing Patients on Statins

Discuss with patients who are on a low or middle intensity statin (refer to Table 2 below) the likely benefits and potential risk of side effects if changed to a high intensity statin when they have a medication review and agree with the person whether a change is needed. In patients who are willing to consider a high intensity statin, the algorithm appropriate for the patient should be followed e.g. Algorithm 1 or 2 as above.

Drug Treatments

Statins

Table 1: Summary of Statin Prescribing - *consider titrating the dose up if >40% reduction in non-HDL-C is not achieved.*

OFFER	USUAL STARTING DOSE
>10% 10 year CVD risk	Atorvastatin 20 mg
Type 2 diabetes (>10% CVD risk)	Atorvastatin 20 mg
Type 1 diabetes (>40 years of age; or >10 year duration; or nephropathy; or other CVD risks)	Atorvastatin 20 mg
CKD	Atorvastatin 20 mg
CVD without CKD	Atorvastatin 80 mg
CONSIDER	
People >85 years	Atorvastatin 20 mg
Type 1 diabetes without additional risk factors	Atorvastatin 20 mg

- The decision to start statins should be made after an informed discussion between the clinicians and the person about the risks and benefits of statin treatment, taking into account factors such as potential benefits from lifestyle modifications.
- NICE has grouped the statins into three intensity categories according to the percentage reduction in LDL-cholesterol. **Atorvastatin** is the 1st line option.
- **Rosuvastatin** (2nd line option) may be considered after treatment with atorvastatin.
- **Simvastatin** (3rd line option) and **Pravastatin** (4th line option) may be considered in patients who are intolerant to atorvastatin and rosuvastatin, or in whom other statins are deemed unsuitable e.g. due to contraindications/interactions.

Table 2: Statin Intensity (as defined by NICE CG181 click here)

Drug	Daily dose (mg)				
	5	10	20	40	80
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	**42%***
Atorvastatin		37%	**43%**	**49%**	**55%**
Rosuvastatin	38%	**43%**	**48%**	**53%**	-
Atorvastatin + Ezetimibe		52%	54%	57%	61%

20 - 30%	**Low intensity**
31 - 40%	**Medium intensity**
Above 40%	**High intensity**

% = percentage reduction in LDL cholesterol

*Advice from the MHRA click here: There is an increased risk of myopathy associated with high dose (80 mg) simvastatin. This dose should only be considered in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

Rosuvastatin (formulary restrictions GREEN)

Local advice is that rosuvastatin may now be used in patients that have contraindications to or do not tolerate atorvastatin.

- Please refer to Algorithm 1 or Algorithm 2 above for dosing.
- In patients who are intolerant to atorvastatin, consideration should be given to lower initial doses of rosuvastatin as per statin intolerance pathway (see Appendix 2).
- The BNF recommends an initial dose of 5 mg in patients >70 years. No other dose adjustment is necessary in relation to age. Clinical judgement should be used for consideration of higher doses dependent on the requirement for a high intensity statin based on clinical diagnosis.

- No dose adjustment is necessary in patients with mild renal impairment.
- The recommended initial dose is 5 mg in patients with moderate renal impairment (creatinine clearance of <60 mL/min). Doses above 20 mg are contraindicated in patients with moderate renal impairment, assessment of renal function should be considered during routine follow-up of these patients.
- Rosuvastatin is contraindicated in patients with severe renal impairment (creatinine clearance of <30 mL/min).
- Maximum dose of rosuvastatin is 20 mg daily for patients taking clopidogrel (see Interactions - Table 4).

Intolerance to statins - For management of statin intolerance, please refer to Appendix 2.

Ezetimibe (also see NICE TA385) (formulary restrictions GREEN)

- For treating primary heterozygous-familial and non-familial hypercholesterolaemia (for heterozygous-familial hypercholesterolaemia see NICE CG71 Familial Hypercholesterolaemia).
- Monotherapy as a treatment option if statin contraindicated or not tolerated.
- In combination with a statin only when lipid levels are not adequately controlled and changing from the initial statin (atorvastatin) is being considered.
- Ezetimibe when combined with any statin is likely to give greater reduction in non-HDL-C/LDL-C than doubling the dose of the statin.

PCSK9 inhibitors - alirocumab and evolocumab (formulary restrictions RED)

NICE TA393 and TA394 recommends alirocumab and evolocumab as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia in **selected patients** after statin and ezetimibe treatment has been optimised. PCSK9 inhibitors alone or in combination with statin or ezetimibe produce an additional LDL-C reduction of approximately 50% (range 25 - 70%).

PCSK9 inhibitor prescribing restrictions. In accordance with the Bucks formulary:

- PCSK9 inhibitors may **only be initiated by a consultant lipidologist or chemical pathologist** and **continued by a lipid specialist prescriber in the Lipid Clinic** (RED on the formulary traffic light list).
- **Ensure the patient's treatment is optimised before considering referral to Lipid Clinic for consideration of PCSK9 inhibitors as follows:**
    - FOR ALL PRESCRIBING - a completed and approved Blueteq (HIGH COST DRUG compliance) form is required.
    - Treatment with the maximum tolerated doses of all formulary statins has been reached AND combination treatment of maximum tolerated dose of statin plus ezetimibe, OR
    - All formulary statins are contraindicated AND
    - Where adherence to treatment has been assessed and confirmed
- PCSK9 inhibitors **are supplied through hospital via homecare**; GPs may be asked to prescribe statin.
- The PSCK9 inhibitors will be considered if LDL-C concentrations are persistently above the recommended levels in the table below, despite maximal tolerated lipid-lowering therapy (as per NICE TA393 and TA394).

Eligibility criteria for consideration of PCSK9 inhibitors

	Without CVD	**With CVD**	
		High risk of CVD [1]	**Very high risk of CVD [2]**
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/L	Recommended only if LDL-C concentration is persistently above 3.5 mmol/L

[1]High risk of cardiovascular disease is defined as a history of any of the following: Acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, peripheral arterial disease.
[2]Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

PCSK9 inhibitors dosing – please see BNF.

Ongoing monitoring:
Patients should be monitored by the Lipid Clinic for efficacy, adherence to treatment, and adverse effects: LDL-C, total cholesterol and liver function tests (LFTs) will be measured. The frequency of monitoring will be:

- 6 weeks after starting treatment
- Annually thereafter

Continuation criteria:
A minimum reduction of 30% in LDL-C is achieved after 3 months and is sustained. NICE have not specified continuation criteria for PCSK9 inhibitors and this criteria is based on the general consensus amongst lipidologists and local expert consultant lipidologist opinion. Consideration should be given to an LDL-C check at 3 months based on this consensus.

Other lipid lowering agents - Fibrates, bile acid sequestrants and omega-3 fatty acid compounds

Do not routinely offer fibrates, bile acid sequestrants and omega-3 fatty acid compounds, alone or in combination with a statin, for the prevention of CVD in any of the following:

- Primary or secondary prevention
- CKD
- Type 1 or type 2 diabetes

Omega-3 fatty acid compound are not on the Bucks joint formulary and are not recommended by NICE as adjuvant treatment in secondary prevention.

Table 3: Statin Monitoring and Follow-up

Tests required	Baseline monitoring and action	Monitoring required after initiating a statin
Full lipid profile Full lipid profile includes: TC, HDL-C, non-HDL-C and triglyceride (fasting sample not required)	• **TC concentration >7.5 mmol/L + family history of premature CHD**[******] **→ consider possibility of familial hypercholesterolaemia** and investigate as per NICE CG71. • **TC >9.0 mmol/L or non-HDL-C >7.5 mmol/L → arrange for specialist assessment** (even in absence of 1st degree family history of premature CHD) • **Triglyceride >20 mmol/L →refer to specialist** (not due to excess alcohol or poor glycaemic control) • **Triglyceride 10 – 20 mmol/L** → repeat with fasting test between 5 - 14 days later and review for secondary causes of hyperlipidaemia ○ If triglyceride remains >10 mmol/L → seek specialist advice • **Triglyceride 4.5 - 9.9 mmol/L** → risk assessment tool may underestimate CVD risk therefore patients should not be risk scored until review. Optimise other risk factors. [******]Family history of premature CHD is defined as male first-degree relatives <55 years of age and female first-degree relatives <65 years of age.	**Measure full lipid profile at 3 months or following dose change. Review patients taking statins annually.** • Aim >40% reduction in non-HDL-C • If <40% reduction in non-HDL-C → check adherence, timing of dose, diet and lifestyle • If >40% reduction still not achieved consider increasing the dose if patient on <80 mg atorvastatin and patient is at high risk of CVD due to comorbidities, QRISK score or based on clinical judgement**.** (Seek specialist advice if eGFR <30 mL/min/1.73 m^2.) There is **no need for annual monitoring** of cholesterol if for primary prevention. Only consider random cholesterol level every 1 - 3 years if for reasons of compliance, patient acceptance, etc.
Creatinine kinase (CK)	• CK is NOT routinely measured before statin initiation. If **persistent generalised unexplained muscle pain** before starting statin and the patient falls in the "at Risk of SRM" group (refer to page 2 the NHSE intolerance pathway for full list, statin-intolerance-pathway-03092020.pdf (england.nhs.uk)), measure ***CK levels at baseline.*** If CK levels are >4x ULN do not start statin - investigation required. Do not measure CK if person is asymptomatic. • If patients develop muscle pain whilst being treated with a statin follow the Statin Intolerance Pathway - statin-intolerance-pathway-03092020.pdf (england.nhs.uk).	• CK is NOT routinely measured if a patient is asymptomatic. • If patients develop muscle pain whilst being treated with a statin follow the Statin Intolerance Pathway - statin-intolerance-pathway-03092020.pdf (england.nhs.uk). (See Appendix 2.) • **Always check for drug interactions.**

Tests required	Baseline monitoring and action	Monitoring required after initiating a statin
Liver transaminases enzymes (LFTs) (alanine aminotransferase (ALT) or aspartate aminotransferase (AST))	• **<3 times ULN → Start statin**	**Measure ALT/AST at 3 months after initiation then within 3 months of every additional up titration and then again at 12 months.** No need to check again after 12 months, unless clinically indicated i.e. signs of hepatotoxicity. • If AST/ALT elevated but <3 times ULN, continue statin and repeat LFTs in 4 - 6 weeks. If AST/ALT remain elevated but <3 times ULN then continue statin and repeat again in 6 months. • If AST/ALT >3 times ULN, discontinue statin, repeat LFTs in 4 - 6 weeks. If LFTs normalise, consider switching statin. Repeat LFTs at 4 - 6 weeks, then again at 3 months. STOP statin if AST/ALTs continue to be ≥3 x ULN and consider specialist opinion.
Other monitoring	HbA1c, renal function and eGFR, thyroid stimulating hormone (TSH). Alcohol consumption, smoking status, blood pressure (BP), BMI.	
	• Discuss adherence and lifestyle modification. • Advise women to stop taking statin if pregnancy is a possibility or 3 months before attempting to conceive.	

Interactions - *Please refer to the current BNF or SPC for a full and up-to-date list of drug interactions*

- Due to increased risk of myopathy, simvastatin is contraindicated or requires dose reduction when used with several classes of interacting medicines (see table below).
- All statins interact with fibrates and this combination poses a higher risk of rhabdomyolysis.
- Several medications interact with both simvastatin and atorvastatin, but not or less significantly with pravastatin. Examples include amiodarone, antifungals e.g. itraconazole, posaconazole, ketoconazole, voriconazole, fluconazole (risk of hepatotoxicity with use of fluconazole or itraconazole with pravastatin), combined oral contraceptives, digoxin, diltiazem, erythromycin and clarithromycin (use erythromycin and clarithromycin with caution with pravastatin), telaprevir, ticagrelor, verapamil, several HIV medicines (e.g. indinavir, nelfinavir, ritonavir, saquinavir), St John's Wort (with caution).

Table 4: Simvastatin, Atorvastatin and Rosuvastatin Drug Interactions
Please refer to the current BNF or SPC for a full and up-to-date list of drug interactions.

Agents	Simvastatin	Atorvastatin	Rosuvastatin
Ketoconazole **Posaconazole** **Erythromycin** **Telithromycin** **Itraconazole** **Clarithromycin**	Contraindicated	Avoid if possible; consider temporary suspension of atorvastatin if interacting drug is taken for a short period. If unavoidable a lower starting and maximum dose of atorvastatin should be considered, and appropriate clinical monitoring is recommended. See SPC for maximum doses.	Both rosuvastatin and itraconazole can increase the risk of hepatotoxicity - avoid if possible. Erythromycin leads to reduced exposure, avoid concomitant use. Telithromycin – monitor for signs of myopathy.
Ciclosporin	Contraindicated	Maximum dose 10 mg daily atorvastatin.	Contraindicated
Danazol	Contraindicated	No specific recommendation	No specific recommendation
HIV protease inhibitors	Contraindicated	Avoid if possible. See SPC for maximum recommended doses.	Avoid if possible. See SPC for maximum recommended doses.
Gemfibrozil	Contraindicated	Lower starting dose and clinical monitoring is recommended	Lower starting dose (5 mg) and clinical monitoring is recommended. A 40 mg dose is contraindicated.
Other fibrates	Do not exceed 10 mg simvastatin daily (except fenofibrate)	Lower starting dose and clinical monitoring is recommended	Lower starting dose (5 mg) and clinical monitoring is recommended. A 40 mg dose is contraindicated.
Ezetimibe	Additive risk of myopathy cannot be ruled out	Additive risk of myopathy cannot be ruled out	Additive risk of myopathy cannot be ruled out
Amlodipine	Do not exceed 20 mg simvastatin daily	No specific recommendation	No specific recommendation
Amiodarone **Verapamil** **Diltiazem**	Do not exceed 20 mg simvastatin daily	Consider lower maximum dose; appropriate clinical monitoring is required	No specific recommendation
Fusidic acid (systemic)	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.	Concurrent use is not recommended. Temporary suspension of atorvastatin may be considered.	Concurrent use is not recommended. Temporary suspension of rosuvastatin may be considered.
Grapefruit juice	Avoid grapefruit juice when taking simvastatin	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended	No specific recommendation
Ticagrelor	Do not exceed 40 mg simvastatin daily	No specific recommendation	No specific recommendation
Clopidogrel	No specific recommendation	No specific recommendation	Do not exceed 20 mg rosuvastatin daily

Acknowledgement

Some content of this guideline was adapted from Derbyshire Joint Area Prescribing Committee Lipid modification guideline.

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Appendix 1: Lifestyle Advice

- At initial assessment and at each review assess modifiable risk factors and the patient's readiness to change
- Give tailored advice in line with NICE Public Health Guidance 6 Behaviour Change https://www.nice.org.uk/guidance/ph6
- For all areas of behaviour change offer brief advice and referral to specialist services if appropriate

Cardioprotective diet

- Advise a reduction in fat intake, replacing saturated fats with mono and polyunsaturated fats such as olive and rapeseed oil
- Increase wholegrain, reduce sugar including fructose, aim for 5 fruits/vegetables per day, 2 portions of fish and 4 - 5 portions of nuts/seeds/pulses per week

Physical Activity

- Advise 150 minutes of moderate intensity or 75 minutes of vigorous intensity aerobic exercise per week
- Advise muscle strengthening exercise on at least 2 days per week
- Agree goals and provide written information in line with NICE Public Health Guidance 2 https://www.nice.org.uk/guidance/PH2

Weight

- Ensure advice is given in line with NICE Guidance 43 https://www.nice.org.uk/guidance/cg43

Alcohol

- Assess using the AUDIT questionnaire
- Advise that the safe limits for alcohol are 14 units per week, over at least 3 days, for men and women

Smoking

- Give advice consistent with NICE Public Health Guidance 10 http://www.nice.org.uk/guidance/ph10
- Provide support and pharmacotherapy for those who do not wish to be referred

Appendix 2: Intolerance to Statins

For patients with intolerance or adverse effects with statins, please refer to the NHS England Statin Intolerance Pathway, found at statin-intolerance-pathway-03092020.pdf (england.nhs.uk).

Adverse effects may include muscle related or non-muscle related side effects.

Myalgia while taking statins: Refer to statin-intolerance-pathway-03092020.pdf (england.nhs.uk)

Non-muscle related side effects: Refer to statin-intolerance-pathway-03092020.pdf (england.nhs.uk)

For non-muscle related side effects, the following principles referred to should be considered:

- Use maximum tolerated dose of statin to treat patients.
- If patients report adverse effects with high intensity statins discuss the following strategies:
  - Stop statin and try again after 6 weeks or when symptoms have resolved to check if symptoms are related to the statin.
  - Reduce the dose within the same intensity group.
  - Change statin to a lower intensity group (see Table 2 Statin Intensity).
- Seek specialist advice regarding other options for treating patients at high risk of CVD (such as those with chronic kidney disease, type 1 diabetes, type 2 diabetes or genetic dyslipidaemias) and those with CVD who are intolerant to trials of generic statins.