NHS
Oxfordshire
Clinical Commissioning Group

Lipid Modification Guidance

Key Points:

- Atorvastatin is the first line statin, usually at 20 mg for primary prevention and 40-80 mg for secondary prevention.
- In primary prevention if CVD risk over 10 years is >20 % offer atorvastatin 20mg. If CVD risk over 10 years is 10-20 % then discuss with patient the pros and cons of statin treatment.
- There is no need actively to switch patients on simvastatin who are treated to target.
- QRISK2 is the tool to use to assess CVD risk (including type 2 diabetes).
- In primary prevention encourage lifestyle modification and review, and then reassess the CVD risk before starting statins.
- In secondary prevention do not delay statin initiation whilst modifying modifiable risk factors.

Who to Consider for Statin Therapy

1. Patients with Clinical Atherosclerotic Disease (Secondary Prevention)

These patients are at highest risk and should be started on a statin. They do not need a QRISK2 assessment. The 2014 NICE CG 181 guidelines suggest **atorvastatin 80mg** as first line treatment for secondary prevention (lower dose if drug interactions, risk of adverse events, patient preference).

Higher risk of adverse effects is present in the elderly, those with low muscle mass or impaired renal function. The lipid lowering difference between 40 and 80 mg atorvastatin is relatively small (on average a 6-8% further reduction in LDL-C concentrations). Insufficient cholesterol lowering, combined hyperlipidaemia (see severe hypertriglyceridaemia below) or statin intolerance may require other or additional treatments. The OCDEM Lipid advice line (oxon.diabetes_lipidsadvice@nhs.net) can be contacted or a referral can be made to the OCDEM Lipid Clinic.

2. Primary Prevention

Encourage lifestyle modification and then review and reassess of CV risk before starting a statin in age 40 to 84 years to reflect CG181. The following links may be useful:

- NICE guideline on Obesity CG 43
- See Healthy Oxfordshire
- NICE pathway: smoking cessation (most important)
- NICE pathway diet
- NICE pathway: behaviour changes
- Physical activity guidelines for adults at NHS choices

For patients 40-84 years with no symptoms of atherosclerotic disease, 2014 NICE lipid modification guidelines recommend a 10 year risk of 10% or more as the threshold for initiation of treatment with atorvastatin 20 mg. At APCO November 2014 it was agreed that caution should be exercised with the 10 year 10% treatment threshold. Patients up to age 84 years who are identified to be at a greater than 20% risk of cardiovascular disease using QRISK2 should be commenced on 20 mg atorvastatin along with receiving appropriate lifestyle advice. If the risk is between 10-20% then lifestyle advice should be given in the first instance with the option of starting on a statin after discussion with the patient.

For patients over 85 years atorvastatin 20 mg should be considered (NICE CG181). Patient preference co-morbidity and harms of poly-pharmacy need to be balanced against any potential benefits.

It should be noted that to prevent one cardiovascular event in people with a 10y CVD risk of 10 % 167 would have to be treated with a statin for 5 years. For a 10 year CVD risk of 20% the number needed to treat is 67.

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There is no definite need to switch patients who are already established on simvastatin 40 mg for primary prevention under the previous "fire and forget" strategy suggested in 2008 NICE guideline. There is also no need to switch those who are adequately treated to target on simvastatin for secondary prevention.

3a. Primary Prevention for People with Type 1 Diabetes

Offer atorvastatin 20 mg for the primary prevention of CVD to adults with type 1 diabetes who:

- Are older than 40 years or
- Have had diabetes for more than 10 years (in adults) or
- Have established nephropathy or
- Have other CVD risk factors

3b. Primary Prevention for People with Type 2 Diabetes

Offer 20 mg atorvastatin for the primary prevention of CVD to people with type 2 diabetes who have a 10 % or greater 10-year risk developing CVD. Estimate the level of risk using the QRISK2 assessment tool. For young patients (aged 20-40 years) with type 2 diabetes, consider using the lipid e-mail advice line: oxon.diabetes_lipidsadvice@nhs.net. Details of family history, BMI/body habitus and clinical presentation would be useful within the information supplied.

4. People with CKD

Consider offering atorvastatin 20 mg for the primary or secondary prevention of CVD to people with CKD. Consider increasing the dose if a greater than 40% reduction in non-HDL cholesterol is not achieved and eGFR is 30 ml/min/1.73m^2 or. Agree the use of higher doses with a renal specialist if eGFR is <30.

5. Familial Hypercholesterolaemia (FH) and Familial Lipid Disorders

Suspect familial hypercholesterolaemia (FH) as a possible diagnosis in adults with:

- a total cholesterol level greater than 7.5 mmol/l and/or
- a personal or family history of premature coronary heart disease* (an event before 60 years in an index individual or first-degree relative).

Systematically search primary care records for people:

- younger than 30 years, with a total cholesterol concentration greater than 7.5 mmol/l and
- 30 years or older, with a total cholesterol concentration greater than 9.0 mmol/

as these are the people who are at highest risk of FH. These patients should be referred to the specialist lipid clinic in line with the NICE QS41 (Sept 2013). High-intensity statins are the first line treatment in FH (NICE 2017) CG 71.

Beware of patients who have first degree relatives with premature heart disease but who do not fulfill FH criteria. These patients could be at high risk in which case e-mail or refer to the lipid clinic (oxon.diabetes_lipidsadvice@nhs.net).

Exclude secondary causes of dyslipidaemia – which might include hypothyroidism, excess alcohol, poorly controlled diabetes, liver and renal disease (nephrotic syndrome) before referral. The lipids email advice line might be useful (oxon.diabetes_lipidsadvice@nhs.net)

6. Severe Hypertriglyceridaemia

If the triglyceride concentration is above 20mmol/l in the absence of excess alcohol or poor glycaemic control, refer to secondary care because of the major concern of the risk of pancreatitis.

If the triglyceride concentration is 10-20 mmol/l repeat the measurement with a fasting test (after an interval of 5 days but within 2 weeks) and review for potential secondary causes. Specialist advice should be sought if the triglyceride level remains above 10mmol/l. If the concentration remains above 5 mmol/ l and cholesterol is also elevated, contact the Lipid advice line (oxon.diabetes_lipidsadvice@nhs.net) or refer the patient to a lipid clinic. Low

threshold for seeking e mail advice/referral if the patient also has a positive family history for premature cardiovascular disease.

Due to the day-to-day variability of triglycerides it is rarely identified as a strong risk factor in epidemiological settings and it is not a parameter in QRISK (though low HDL may reflect high triglycerides), but recent evidence suggest triglycerides is causally related to cardiovascular disease. Low HDL-C is not causally related to cardiovascular disease.

SUGGESTED PATHOLOGY TEST REQUIREMENTS ASSOCIATED WITH STATIN PRESCRIBING		
LIPID PROFILE (Total cholesterol, HDL, Non-HDL and triglycerides)	Before starting statin	For Secondary prevention only one reading is needed of total cholesterol, HDL and non-HDL cholesterol and triglycerides, ideally before treatment, for reference purposes. For primary prevention, check total cholesterol, HDL and non-HDL cholesterol, and triglycerides. If Triglyceride level is above 5mmol/l, recheck fasting lipids.
	After starting statin	For secondary prevention (e.g. atorvastatin 40-80mg), check a lipid profile 3 months after starting treatment, aiming for a 40% reduction in **non-HDL cholesterol** (NICE 2014). For primary prevention (atorvastatin 20mg), option of a "fire and forget approach" (NICE 2008) or recheck a lipid profile 3 months after starting treatment (NICE 2014). If the latter, aim for a 40% reduction in non-HDL cholesterol. If not achieved, review compliance and lifestyle factors, and consider increasing dose of atorvastatin to 40mg.
LFTs	Before starting statin	Check LFTs. In the absence of known liver disease, statin can be started if ALT is < 3X upper limit of normal. Do not exclude statin usage if ALT raised but < 3X upper limit of normal (ULN). If patient is known to have significant liver disease or if ALT > 3X ULN, and statin felt indicated for secondary prevention, seek specialist advice before commencing statin
	After starting statin	No need to recheck in patients at low risk of liver disease and normal baseline LFTS unless there is a clinical indication or on very high dose (Atorvastatin 80mg). If at risk of liver disease, or started on Atorvastatin 80mg, LFTs do need checking, typically at 2-3 months, and then 6-12 months after starting. If ALT is already raised when starting, an earlier check on LFTs, perhaps at 4-6 weeks, would seem prudent. If ALT is > 3x ULN, stop the statin and check the ALT again in a few weeks. Assuming it normalizes, a different statin can be tried with careful monitoring of LFTs.
Creatinine Kinase	Before starting	No need to check CK unless considered at risk of increased muscle toxicity.
	After starting	Check CK only if patient develops myalgia or muscle tenderness whilst considering other causes. Muscle aching in the absence of a rise in CK is not an absolute reason to stop the statin but will depend on person wish to tolerate the symptoms. Consider trying a lower dose of the preferred statin or an alternative statin. A CK > 10X ULN is considered a contraindication to further statin therapy. If CK risen but < 5X ULN continue statin if symptoms allow but monitor CK and symptoms. If CK > 5X ULN (But <10X ULN), stop statin, check renal function and recheck CK again in 2-4 weeks. Seek specialist advice before re-exposing to a statin.
Renal function	Before starting	Check creatinine and electrolytes prior to starting a statin. Atorvastatin has hepatic excretion and is favoured over higher dose simvastatin if renal impairment
	After starting	Check creatinine and electrolytes after 3-5 years

TSH and Glucose/ HbA1c	Check TSH before starting, especially if raised triglycerides. No need to recheck unless clinical indication. Check HbA1c or fasting glucose before commencing statin. No formal recommendation exists for rechecking, but be aware of increased risk of diabetes mellitus with statin usage (dose dependent). Perhaps monitor 3-5 yearly if normal, or annually if impaired fasting glycaemia or HbA1c 6 – 6.5%

Statin Choice

Pravastatin, up to 40mg, is a third line alternative for primary prevention and rosuvastatin is a third line option for secondary prevention. See table below to show comparable intensities.

Table 1 showing stains grouped into three intensity categories according to the percentage reduction in LDL-cholesterol

	Daily Dose (mg)				
Drug	**5**	**10**	**20**	**40**	**80**
Fluvastatin	N/A	N/A	21%	**27%**	**33%**
Pravastatin	N/A	20%	24%	29%	N/A
Simvastatin	N/A	27%	32%	37%	42%*
Atorvastatin	N/A	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	N/A

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

*Simvastatin **80 mg** is not recommended - MHRA warning

Intolerance of statins

If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. Any statin (even lower doses) is preferred to none. If adverse events are reported when taking high-intensity statin discuss the following strategies:

- Critically evaluate possible side effects which typically should be symmetrical muscle aches involving large muscle groups.
- Stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- Reducing the dose of the same statin eg 20 mg to 10 mg atorvastatin
- Changing to another statin at a low dose
- Increasing the dose interval of the statin (only meaningful for atorvastatin and rosuvastatin)

Seek specialist advice about options for treating people at high risk of CVD such as those with CKD, type 1 diabetes type 2 diabetes or genetic dyslipidaemias, and those with CVD, who are intolerant to 3 different statins.

Fibrates eg bezafibrate 400mg and fenofibrate 267 mg

Do not offer a combination of a fibrate with a statin (NICE CG 181). However this combination may be used for particular patients groups after secondary care advice, notably those with a genetic/inherited condition. The combination of statin and fibrate may increase the risks of side effects including rhabdomyolysis.

Ezetimibe

Decision to start ezetimibe should be made in conjunction with specialist advice as for fibrates. NICE TA 385 (which replaces TA132) recommends ezetimibe, alone, as an option for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia in adult patients in whom initial statin therapy is contraindicated, or who are intolerant of initial statin therapy. Ezetimibe, in combination with initial statin therapy, is also recommended as an option for the treatment of primary (heterozygous-familial or non-familial) hypercholesterolaemia in adult patients when:

- serum total or low-density lipoprotein (LDL) cholesterol concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy **and**
- a change from initial statin therapy to an alternative statin is being considered.

When prescribing ezetimibe in combination with statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.

PCSK9 inhibitors

This is a new class of cholesterol lowering drugs (alirocumab and evolocumab) with potent lipid lowering effect recently appraised by NICE (TA393 and TA394). They are given as subcutaneous injection once a fortnight to high risk patients who have insufficient cholesterol lowering by conventional methods (statins, ezetimibe etc). Only prescribed by lipid specialists (oxon.diabetes_lipidsadvice@nhs.net)

Do NOT offer for lipid modification:

- nicotinic acid
- co-enzyme Q10
- vitamin D
- Omega 3 – do not prescribe in line with Thames Valley Priorities Committee Commissioning Policy No. 281 - NICE 'Do Not Do' recommendations.
- bile acid sequestrant (colesevelam, colestyramine and colestipol). However, a bile acid sequestrant may be used for particular patients groups after secondary care advice (oxon.diabetes_lipidsadvice@nhs.net or through referral to the OCDEM Lipid Clinic), notably those with a genetic /inherited condition as listed above).