Royal Wolverhampton Hospital Adult Lipid Lowering Therapy Guidelines 2013 Update

This guideline is intended to assist rational and cost-effective prescribing of lipid regulating medications across both primary and secondary care. It represents an evidence based consensus of opinion of healthcare professionals involved in prescribing lipid regulating therapy.

Before any treatment is initiated, the following lifestyle advice should be given regarding:

- Smoking cessation
- Diet
- Alcohol intake
- Exercise, in particular increasing aerobic exercise activity.

The following should also be addressed:

- Optimisation of blood pressure management in hypertensive patients.
- Optimisation of glycaemic control in patients with diabetes.
- Exclusion of secondary causes of hyperlipidaemia, including diabetes, hypothyroidism, nephrotic syndrome, renal disease, excessive alcohol intake.

1. Lipid Lowering Therapy for the Prevention of Coronary Heart Disease

Primary Prevention

Primary prevention is appropriate for patients <u>without</u> known cardiovascular (CV) disease who have:

1. A calculated CV risk ≥20% over the next 10 years.
2. Familial Hypercholesterolaemia (see familial hypercholesterolaemia)
3. Diabetes
   - People with diabetes are known to be at increased risk of cardiovascular events; this risk is deemed to be high enough to justify the initiation of lipid lowering therapy without further assessment in nearly all patients with type 2 diabetes .[(3)]
   - In diabetes, initiation of a statin may be considered at an earlier age (<40yrs) for individuals where there are multiple cardiovascular risk factors.
   - For diabetic patients not considered to be at high cardiovascular risk, that is not overweight, normotensive (BP<140/80), not on anti-hypertensives, non-smokers, no microalbuminuria,no personal or family history of cardiovascular disease and low risk lipid profile (normal serum HDL cholesterol and triglycerides), cardiovascular risk should be assessed using the UKPDS risk engine as outlined in NICE Clinical Guideline 66 and reviewed on an annual basis.

For more information, please refer to cardiovascular risk assessment and management in diabetes:http://www.wdconline.org.uk/12_management_guidelines/12_management_guidelines.htm

Primary prevention for patients <u>with a</u> calculated CV risk ≥20% over the next 10 years

Step 1: Lifestyle advice should be issued prior to consideration of statin therapy

Lifestyle advice regarding smoking cessation, diet, exercise and reducing alcohol consumption should be offered.
Dietary modifications alone can reduce serum cholesterol by approximately 5%.[(1)]

Step 2: Atorvastatin 20mg daily/Simvastatin 40mg nocte

If cholesterol levels remain elevated despite appropriate lifestyle and dietary modifications, lipid lowering therapy may be initiated.

Step 3: For patients who are still not able to achieve their target cholesterol levels:

- Check compliance
- Consider dose optimisation to Atorvastatin 40mg daily

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Secondary Prevention

Secondary Prevention is appropriate for patients with known CV disease (coronary artery disease/ischaemic stroke/TIA or peripheral vascular disease)

Step 1: Lifestyle advice should be issued prior to consideration of statin therapy

Lifestyle advice regarding smoking cessation, diet, exercise and reducing alcohol consumption should be offered.
Dietary modifications alone can reduce serum cholesterol by approximately 5%.[(1)]
Manage other cardiovascular factors

If cholesterol levels remain elevated despite appropriate lifestyle and dietary modifications, lipid lowering therapy may be initiated.

Step 2: Atorvastatin 20mg daily/Simvastatin 40mg nocte

Step 3: For patients who are still not able to achieve their target cholesterol levels:
- Check compliance
- Consider dose optimisation to Atorvastatin 40mg daily

Once treatment has been initiated assess the patients lipid profile (together with other modifiable risk factors and any new diagnosis of cardiovascular disease), 1 – 3 months after starting treatment and annually thereafter.

Step 4: Should cholesterol levels still remain elevated, consideration should be given to:
- Optimisation to Atorvastatin 80mg od OR
- Addition of Ezetemibe 10mg od

Ezetemibe can be considered as an adjunct in patients failing to achieve treatment targets despite maximal statin dose or where higher statin doses are not tolerated. If targets are still not achieved with a statin plus Ezetemibe, the patient should be referred to a Specialist for the possible addition of a fibrate. Concurrent prescribing of statins with fibrates increases the likelihood of myopathy/rhabdomylosis and therefore should be undertaken under specialist supervision.

Acute Coronary Syndrome

Intensive lipid lowering therapy is recommended by NICE for all patients following an acute coronary syndrome (including ST elevation MI, non-ST elevation MI and Unstable Angina)

Step 1: Atorvastatin 40mg – 80mg daily

The default statin should be Atorvastatin 80mg daily in addition to dietary advice and lifestyle modifications delivered as part of a local cardiac rehabilitation programme.

For older patients or those with reduced body weight, a lower dose of Atorvastatin 40mg daily may be prescribed.

Step 2: In patients not achieving an average TC≤4.0mmol/L or LDL-C ≤2.0mmol/L on high intensity lipid lowering therapy,
- Check compliance.
- Consider referral for specialist advice.

Targets – Secondary Prevention
The Joint British Societies[4] advise that in all high risk people, rigorous control of blood cholesterol is recommended with the following treatment targets:

- The optimal total cholesterol (TC) target is , 4.0 mmol/l and low density lipoprotein cholesterol ((LDL-C), 2.0 mmol/l, or
- A 25% reduction in TC and a 30% reduction in LDL-C
- Or whichever gets the person to the lowest absolute value.

High Intensity Lipid Lowering
Although NICE guidance recommends Simvastatin 80mg nocte as the default statin of choice for more 'aggressive lipid lowering' in the context of acute coronary syndrome; the use of high dose Simvastatin is associated with an increased incidence of rhabdomylosis and myopathy. In addition, the SEARCH study[5] has shown that increasing doses of Simvastatin from 20mg to 80mg leads to only a 0.3mM reduction in LDL cholesterol. Many patients who present following a myocardial infarction will have elevated baseline total cholesterol and LDL cholesterol, therefore, increasing to or prescribing Simvastatin 80mg daily will not facilitate achieving secondary prevention targets of 4:2 respectively.
With the introduction of generic Atorvastatin, we are now able to treat patients with more aggressive lipid lowering therapy, that is now of a similar acquisition cost to Simvastatin 80mg daily.

MHRA advice regarding high dose Simvastatin[6]

- Prescribers treating patients who are taking Simvastatin 80mg or who are being considered for up-titration to that dose may need to review their treatment during the next visit, to take into account the new evidence, as outlined above.
- Patients who are currently taking Simvastatin 80mg should not stop taking their medicine. However, they should be advised to contact their doctor immediately if they experience unexplained muscle pain, tenderness or weakness.

As outlined in the JBS2 Guidelines, the management of CVD prevention in clinical practice should focus equally on:

(i) people with established atherosclerotic CVD,
(ii) people with diabetes, and
(iii) apparently healthy individuals at high risk (CVD risk of > 20% over 10 years) of developing symptomatic atherosclerotic disease.

This is because they are all people at high risk of CVD. The object of CVD prevention in these high risk people is the same — namely, to reduce the risk of a non-fatal or fatal atherosclerotic cardiovascular event and to improve both quality and length of life. This can be achieved through lifestyle and risk factor interventions and appropriate drug therapies to lower blood pressure, modify lipids, and reduce glycaemia.[4]

Alternative Treatment Options

For patients who are intolerant of statins, alternative treatment options include:

- Fenofibrate 200mg daily OR
- Ezetemibe 10mg daily as monotherapy OR
- Cholestyramine 12-24g daily in divided doses. Other drugs should be taken at least one hour before or four hours after Cholestyramine to reduce the possible interference with absorption.
- The concomitant use of Ezetemibe with Fibrates increases the risk of cholelithiasis and gall bladder disease.[7]

Of note, Ezetemibe does not have large scale trial data to support reductions in cardiovascular events. A placebo controlled study designed to demonstrate a reduction in combined aortic valve events and cardiovascular events in asymptomatic stenosis of the aortic valve (SEAS), failed to demonstrate a significant difference between active treatment and placebo in the primary outcome group. This study unexpectedly showed an increase in cancers and deaths from cancer, although the absolute numbers involved was small and no trend towards a particular cancer being increased was found.[8]

Monitoring Statin Therapy[7][9]

Lipid Levels Total cholesterol (TC) High density lipoprotein (HDL) Low density lipoprotein (LDL) Triglycerides	**Primary Prevention:** routine monitoring of lipid levels is not recommended, although clinicians should consider checking lipid levels occasionally throughout treatment to ensure on-going adherence to therapy. **Secondary Prevention:** Lipid levels should be measured before therapy is initiated; at 12 weeks following initiation or change of dose and at 12 monthly intervals thereafter. If total cholesterol remains persistently raised despite optimising statin therapy.
Thyroid Function Tests	Check before initiating a statin to exclude hypothyroidism
Renal Function	Simvastatin doses above 10 mg daily should be used with caution if eGFR less than 30 mL/minute.
Liver Function Tests (LFTs)	Baseline liver enzymes should be measured before starting a statin. Liver function (transaminases) should be measured within 3 months of starting treatment and at 12 monthly intervals thereafter. If transaminases >3x upper limit of normal (ULN) discontinue statin and refer. For lesser increases in transaminases, which remain elevated at 6 months consider specialist advice.
Creatine kinase (CK)	Routine CK monitoring after initiation is not recommended. CK should be measured during treatment when clinically indicated – i.e. where there are symptoms of muscle pain or tenderness, muscle weakness or muscle cramps. **Patients should be counselled on initiation of statin to report any unusual muscle pain, tenderness or weakness during treatment** **IF MYOSITIS IS PRESENT OR SUSPECTED DISCONTINUE IMMEDIATELY** If muscle soreness occurs: • Rule out common causes (e.g. exercise) • Check TFTs (hypothyroidism predisposes to myopathy) • Measure CK - If CK elevated > 5 x ULN stop and seek advice - If CK elevated < 5 x ULN a) Monitor carefully by repeating CK level in one month b) If remains elevated, reduce dose and recheck CK level in one month c) If still remains elevated consider seeking advice If symptoms continue STOP statin and consult a specialist before re-initiating *Note: Some Black African and Caribbeans have elevated baseline levels of CK. This is not a contra-indication to statin therapy. In these patients, after initiation if the CK > 5 x baseline - seek advice*
Other adverse effects	Headache, dyspepsia or insomnia. Evaluate symptoms at each visit. If symptoms not tolerated: • Consider changing time of dose (after food if nauseous, morning if sleep disturbed) • Consider decreasing dose • Consider using an alternative agent

Statin Interactions[6][10]

Interacting Agents	Prescribing Recommendation
Potent CYP3A4 Inhibitors e.g. HIV protease inhibitors Azole antifungal agents Macrolides Fusidic Acid	Avoid Simvastatin and Atorvastatin Consider usual doses of Rosuvastatin or Pravastatin. For short course treatments of antibiotics or antifungals, stop the statin for the duration of antibiotic treatment and restart later. For patients treated with Fusidic Acid, statin therapy should resume seven days after course completion.
Ciclosporin Gemfibrozil Danazol	Simvastatin is contraindicated
Amiodarone Amlodipine Verapamil Diltiazem	Do not exceed Simvastatin 20mg; higher doses will increase the likelihood of myopathy/rhabdomylosis.
Niacin > 1g daily	Do not exceed Simvastatin 10mg
Grapefruit Juice	Avoid grapefruit juice while taking Simvastatin or Atorvastatin.

2. Lipid Lowering Therapy for the Management of Moderate to Severe Hypertriglyceridaemia.

A fasting serum triglyceride concentration below 2.0mmol/l is normal. In the range of 2.0-6.0mmol/L no specific intervention will be needed unless there are co-existing cardiovascular risk factors, and in particular a strong family history of early cardiovascular death.[11][12]

Patients should be given advice regarding weight loss and correction of any other modifiable cardiovascular risk factors they may have.[11]

Serum triglyceride levels > 6.0mmol/L carry a risk of acute pancreatitis and retinal vein thrombosis. Patients should be advised to reduce their weight if overweight and start a formal lipid lowering diet.[11]

A proportion of patients may have hypertriglyceademia secondary to even moderate alcohol intake. If hypertriglyceridaemia persists, lipid levels should be measured before and after a 4-week interval of complete abstinence from alcohol. If a considerable improvement results, lifelong abstinence should be considered.
Other drugs, such as thiazides, oestrogens and glucocorticoids, may have a similar effect to alcohol in susceptible patients.[11][12]

If the triglyceride levels remain elevated above 6.0mmol/L, despite the above measures, drug therapy is warranted.

Treatment Options:

1. A fibric acid derivative is the agent of first choice.
2. Fish oil capsules which contain omega-3 long chain fatty acids are also effective in lowering triglyceride concentrations.
3. Nicotinic acid may be used in addition, but its side effects are often a problem.

First Line Treatment
Fenofibrate 200mg daily

Monitoring Fibrate Therapy

Monitor LFTs at beginning of treatment and at 1-3 months, 6 months, 12 months, then annually.
Check CK if patient complains of musculoskeletal symptoms.
Discontinue Fibrate is ALT persists > 3 x ULN, or serum Creatinine continues to rise progressively.

It is often difficult to normalize serum triglycerides.

Successful treatment of triglycerides may paradoxically increase total and LDL cholesterol.

If, after fibrate therapy, serum cholesterol is persistently > 5mmol/L in patients with established or at high risk of developing CVD consider specialist referral for additive statin therapy.

If, after fibrate therapy, serum triglycerides are persistently > 5mmol/L consider referral for addition of a statin and/or fish oils.

3. Lipid Lowering Therapy for the Management of Familial Hypercholesterolaemia

Guidelines for the diagnosis and management of FH were published by NICE in 2008.[13]

A clinical diagnosis of FH should be suspected in adults who have markedly elevated total cholesterol (>7.5mmol/L), particularly if there is a positive family or personal history of premature coronary artery disease (CAD)..

Clinical diagnosis of definite or possible FH is based on the Simon Broome Criteria:[12]

Definite FH

- TC> 7.5mmol/L (LDL > 4.9mmol/L), pretreatment (or highest on treatment), and presence of tendon xanthomas in the patient or first/second degree relative. OR
- DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Possible FH

- TC>7.5mmol/L (LDL > 4.9mmol/L), pretreatment (or highest on treatment)

And one of the following:

- Family history of MI (<50 years in 2nd-degree relative or < 60 years in first degree relative)
- Family history of raised cholesterol (>7.5mmol/L in adult 1st or 2nd-degree relative; >6.7mmol/L in child or sibling aged < 16 years)

Patients with suspected or confirmed FH should be referred to a specialist lipid clinic and cascade testing of relatives.

First line treatment is with statins, aiming for ≥50% reduction in LDL-c, although dual treatment with a statin and Ezetemibe may be required to meet this target.
If initial treatment is contra-indicated, not tolerated or ineffective, fibrates, bile acid sequestrants, and nicotinic acid may be initiated by a specialist in FH.

Treatment Options(13)

<table>
<tr><th>Drug Therapy</th><th colspan="2"></th></tr>
<tr><td rowspan="2">Statins</td><td colspan="2">- Use as initial treatment
- To achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline:
➢ Consider prescribing a high-intensity statin
➢ Increase to the maximum licensed or tolerated dose
- When an adult who does not have coronary heart disease, is diagnosed with FH after the age of 60 years, offer a statin with a low acquisition cost.</td></tr>
<tr><td colspan="2">- Measure baseline liver and muscle enzymes (including transaminases and creatine kinase) before starting treatment.
- Raised liver or muscle enzymes should not routinely exclude a person from therapy.
- Do not routinely monitor creatine kinase levels in asymptomatic patients.</td></tr>
<tr><td>Ezetemibe</td><td colspan="2">- Is an option for adults with heterozygous FH if statins are contra-indicated or not tolerated.
- Is an option for adults with heterozygous FH when co-administered with initial statin therapy, If:
➢ Serum or LDL-C concentration is not appropriately controlled with initial statin therapy after appropriate dose optimization or because of intolerance to the statin, and
➢ Consideration is being given to changing from initial statin therapy to an alternative statin.</td></tr>
<tr><td>Bile Acid Sequestrant</td><td>- For long-term treatment, consider offering fat-soluble vitamins (A,D and K) and Folic Acid supplementation.</td><td rowspan="3">- Consider if statin or Ezetemibe are contra-indicated or not tolerated.
- Offer a referral to a specialist in FH for consideration of this treatment.
- The specialist should make the decision as to whether any of these treatments should be added to initial statin therapy.</td></tr>
<tr><td>Fibrate</td><td>- Do not use Gemfibrozil and statins together.</td></tr>
<tr><td>Nicotinic Acid</td><td>- Offer advice on strategies that reduce flushing, including taking:
➢ Low initial doses with meals, and/or
➢ Aspirin 75mg 30 minutes before first daily dose.</td></tr>
</table>

References

(1) Cleemant JL, Lenfant C, The National Cholesterol Education Programme. Progress and Prospects. JAMA 1998;290:2099-2104
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(9) http://www.medicines.org.uk<accessed 03/09/12>
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(12) Ramrakha P, Hill J. Oxford Handbook of Cardiology 2nd Edition. Oxford 2012
(13) NICE Clinical Guideline 71: Familial Hypercholesterolaemia (2008)