Lipid-regulating Drugs (including Statins)

Lipid-regulating drugs are used to treat dyslipidaemias, primarily raised cholesterol. Hypercholesterolaemia is a major cause of atherosclerosis and contributes to the high levels of mortality and morbidity in the UK due to cardiovascular disease (CVD). It is important as one of the three main modifiable risk factors for CVD (the others being smoking and hypertension).

Patients often ask what a ‘normal’ or ‘healthy’ serum cholesterol should be. Unfortunately, there is no clear dividing line between what constitutes a safe level and what constitutes an unsafe level; rather, a continuous spectrum from low to higher risk, along which an individual’s cholesterol, should be interpreted in context with their other cardiovascular risk factors.

Causes of dyslipidaemia
See the separate Hyperlipidaemia article.

Prevention of cardiovascular disease
See the separate Prevention of Cardiovascular Disease and Cardiovascular Risk Assessment articles.

Statins
(Or 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors)

The statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin) competitively inhibit HMG-CoA reductase. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but are less effective than fibrates in reducing triglyceride concentration.

Mode of action and indications
- Competitive inhibitors of the rate-limiting step of hepatic cholesterol synthesis. With a reduced cholesterol pool in the liver, LDL receptor expression is upregulated and increased LDL uptake from plasma takes place, lowering plasma LDL-C. This protects against the development of atheroma and there is a firm evidence base for their use in both primary and secondary prevention of CVD. The risk reduction in primary and secondary prevention is about the same. Since the risk is by definition higher in secondary prevention, the benefit of statins is greater in this scenario than in primary prevention.
- Statins are also thought to have non-cholesterol-related effects such as restoring/improving endothelial function, and anti-inflammatory properties. These are implicated in benefits seen when use of statins is initiated early following an acute myocardial infarction, after percutaneous coronary angiography and in acute coronary syndrome (ACS).
- Statins have a role to play in the regression of atheroma. They reduce the lipid content of plaques and stabilise them through the formation of fibrous caps and microcalcification.
- Statins may also reduce the risk of developing atrial fibrillation.

Who should be on a statin?
National Institute for Health and Care Excellence (NiCE) guidelines suggest that statins should be prescribed:

- To all adults with:
  - A history of CVD, including angina, acute myocardial infarction, acute coronary syndrome, stroke, transient ischaemic attack (TIA) and peripheral arterial disease (secondary prevention).
  - Monogenic lipid disorder - eg, familial hypercholesterolaemia (FH).

- For primary prevention:
  - All those aged up to 84 years who have a 10-year risk of CVD of 10% or more as measured by the QRISK2 risk assessment tool, if lifestyle measures have been ineffective.
  - All those aged 85 years and over by virtue of age alone, unless comorbidities, patient preference or contraindications make this inappropriate.
  - All adults with type 1 diabetes who are aged over 40 years or have had diabetes for more than 10 years, or have established nephropathy or have other cardiovascular risk factors.
  - Atorvastatin should be used for primary or secondary prevention of CVD for people with chronic kidney disease (CKD).
  - In the past there has been much debate as to the long-term benefits versus risk of statins in primary prevention. A Cochrane review has confirmed a reduction in all-cause mortality, vascular events and revascularisations. A more recent Irish review concluded that the evidence for the effectiveness of statins in primary prevention was mixed. A discussion should be held with individual patients about the degree of risk reduction weighed against the potential side effects.

In some situations, statin treatment should be initiated without recourse to formal estimation of cardiovascular risk. These include:

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Those with diabetes at any age with additional risk factors - eg, hypertension, metabolic syndrome, TChol >6 mmol/L or a strong family history.
Those with renal dysfunction, including diabetic neuropathy.
Where the ratio of TChol:HDL is 6 or more.

NICE suggests that "a systematic strategy should be used to identify people aged 40-74 years who are likely to be at high risk", effectively advocating screening in this age group to identify those likely to benefit from statin therapy and other interventions.

Lipid dysfunction is an early feature of type 2 diabetes but further research is required to elucidate the risk:benefit ratio of individuals with low CVD risk\[11\].

**Side-effects**\[2\]
Statins are usually well tolerated. Side-effects may including fatigue, headache, nausea, indigestion or change in bowel habit. Important but rarer side-effects include:

**Muscle effects**\[12, 13, 14\]
- The most important adverse effect of these drugs is myalgia characterised by muscle and tendon pain, stiffness, muscle weakness and cramping. This affects 5-10% of patients taking statins.
- Statin-induced myopathy includes a spectrum from asymptomatic increase in serum creatine kinase (CK) to myalgia, myositis and, most seriously, rhabdomyolysis. Rhabdomyolysis is rare (0.1 per 10,000 treatment years) but potentially life-threatening.
- Mean duration of treatment prior to onset of symptoms is six months. Muscle symptoms that develop in a patient who has been on statins over several years are unlikely to be due to the drugs.

Risk of myopathy is increased with:
- Underlying muscle disorders.
- Multisystem diseases (eg, diabetes).
- Renal or liver impairment.
- Untreated hypothyroidism.
- Vigorous exercise.
- Intercurrent illness.
- Major surgery or trauma.
- Alcohol abuse.
- Age over 70 years.
- Co-prescription with other lipid-lowering drugs.
- Past history of myopathy with any lipid-lowering drug.
- Co-prescription of drugs that inhibit cytochrome P450 CYP3AE (eg, fibrates, nicotinic acid, calcium-channel blockers, ciclosporin, amiodarone, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin).
- Diet - intake of grapefruit (simvastatin, atorvastatin and lovastatin) or cranberry juice (fluvastatin).

- Genetic factors, such as polymorphisms in cytochrome P450 isoenzymes, that increase the risk of statin-induced myopathy are increasingly being identified and may become more important in the future\[15\].

**Hepatotoxicity**
Rare and dose-dependent and usually reversible. Statins should not be withheld in patients with high cardiovascular risk who have raised transaminases of no clinical relevance or who have stable hepatic disease - decisions should be made on an individual basis.

**Statin-induced diabetes**
Observational studies and meta-analyses have revealed a recognised link between statin use and new-onset diabetes. The figure has been assessed as between 10-12%. The mechanism is thought to involve insulin resistance and insulin secretion. Current evidence suggests that this risk is far outweighed by the beneficial effects that statins exert on hyperlipidaemia\[16\].

One retrospective study found the prevalence of statin-induced new onset of diabetes to be 7.03%. The main risk factors identified were age (≥60 years), rosuvastatin therapy, higher dose and longer duration of statin therapy.

**Targets**
Current NICE guidance does not recommend a lipid target for primary prevention\[7\]. However, it recommends that for patients with a 10% or greater 10-year CVD risk, initial treatment should be with the high-intensity statin atorvastatin 20 mg a day, unless this is not suitable due to contra-indications, high risk of side-effects, drug interactions or patient preference.

There is no specific guideline within NICE for secondary prevention, but it recommends atorvastatin 80 mg a day, unless this is not suitable.
High-intensity statins are defined as those which reduce LDL cholesterol by at least 40%. A prospective cohort study of over 165,000 primary care patients has shown that 51% do not reduce their LDL by at least 40% even after two years of statin therapy. Patients prescribed low-intensity statins were less likely to reach target than those prescribed high-intensity statins. When adjusted for age and baseline LDL, patients who did not reach target were 22% more likely to have a CVD event over 6.2 years of follow-up[17].

The current high-intensity statin regimes are:

- Atorvastatin: 20-80 mg
- Rosuvastatin: 10-40 mg
- Simvastatin: 80 mg

Other medical societies have suggested progressively lower targets of LDL-C in recent years - eg, the European Society of Cardiology recommends an LDL-C <70 mg/dL in patients for secondary prevention in patients with known coronary artery disease. One study reported that whilst patients achieved this target initially, this was attenuated over time, possibly due to issues of compliance with intensive regimes by patients and physicians[18].

Initiating and monitoring treatment
Choosing a statin[7]

Before starting lipid modification therapy for primary prevention of CVD, a blood test for full lipid profile should be taken (total cholesterol, HDL cholesterol, non-HDL cholesterol and triglycerides.

- NICE currently recommends atorvastatin 20 mg daily as the first-choice drug for primary prevention and atorvastatin 80 mg daily for secondary prevention.
- Where this is not tolerated, suggested alternatives are:
  - Dose reduction of statin.
  - Switching to an alternative statin preparation.

Biochemistry[7]

- Check lipids (fasting specimens required to quantify LDL fraction and triglycerides (TGs) accurately) and LFTs prior to starting treatment.
- Exclude any secondary causes of hypercholesterolaemia (eg, hypothyroidism) or, if present, ensure maximally treated before commencing specific lipid-lowering therapy.
- There is no need to measure CK prior to initiating statin therapy unless the patient is complaining of generalised muscle pains. If the CK is >5 times upper limit of normal, re-test after seven days. If the level remains >5 times upper limit of normal, do not prescribe a statin. If CK is raised but <5 times upper limit of normal, prescribe a statin, but in the lower-dose range.
- Measure CK and TFTs urgently if a patient reports muscle pain and stop the drug whilst this is investigated.
- Do not routinely monitor CK unless clinically indicated:

Where CK is[19]:

- **Normal**: this is myalgia. Continue a statin where symptoms are tolerable and not progressive. If intolerable, stop and consider an alternative statin challenge or alternative lipid-lowering therapy.
- **<10 x upper limit of normal (ULN)**: this is myositis. Again, continue if symptoms are tolerable or stop and consider alternatives if not. Where muscular symptoms or raised CK continue to persist, refer for electromyography and/or muscle biopsy.
- **>10 x ULN**: this is rhabdomyolysis. Statin therapy should be discontinued. Be suspicious clinically of this situation, where the patient has brown urine. Check renal function and urine myoglobin. An alternative lipid-lowering drug should be considered and re-exposure to statins only after a careful risk:benefit analysis.

- If the CK level is less than 10 x the upper limit then a low dose of the same or different statin can be tried. If myalgia returns then ezetimibe monotherapy can be tried. Ezetimibe can also be combined with a low-dose statin to help achieve target cholesterol levels[20].
- Repeat LFTs after three months of treatment, after any further dose increases and at a year. Do not repeat again unless clinically indicated:

- **A rise in aspartate transaminase (AST) and alanine aminotransferase (ALT) <3 x ULN** - relatively common, reported in 1-2% of patients and usually occurs in the first three months. Do not routinely stop statin treatment at this level.
- **A rise in transaminases >3 x ULN** - stop the statin temporarily before rechallenging or reduce the dose with closer monitoring.

Reaching lipid targets[7][10]
For people on a high-intensity statin, a full lipid profile should be measured after three months of treatment (both primary and secondary prevention) and the target should be a greater than 40% reduction in non-HDL cholesterol. Do not forget concordance. Many patients stop taking statins altogether within a year or take them at less than the prescribed dose. Statins need to be taken in the long term (over years) to derive the fullest benefit. A Cochrane Review looking at improving concordance with lipid-lowering medication found that intensification of patient intervention improved compliance in the long- and short-term. Effective interventions included electronic reminders, pharmacist-led interventions, healthcare professional education of patients, improved patient information and education, telephone reminders and simplifying drug regimens [21].

Patient advice[10]
Good patient information and education improve compliance. Important messages to get across include:

- These drugs reduce cardiovascular risk. In the case of primary prevention, we are not treating established disease and an individual’s perception of their risk will alter the likelihood of their taking the drug therapy as prescribed.
- Offer clear information regarding an individual’s absolute risk of CVD and about the absolute benefits and harms of an intervention over a 10-year period. Decision-making aids are available.
- These drugs need to be taken as ongoing medications. Stopping them will result in the loss of benefit.
- Serious side-effects are unlikely but if muscle pain or weakness is experienced, this should be reported immediately to the doctor.
- These drugs may have multiple interactions, both with prescribed medication, over-the-counter remedies (eg, St John’s wort) and non-drugs (eg, grapefruit juice). Always seek advice.
- Take statins at night when they have a slightly greater effect.

Statins in children[22]
NICE recommends considering the use of lipid-modifying drugs in children with familial hypercholesterolaemia by the age of 10. Consideration should be given to:

- Age.
- Age of onset of coronary heart disease within the family.
- Presence of other cardiovascular risk factors, including their LDL-C concentration.

Treatment should be initiated by a specialist.

Studies suggest that in the case of statin treatment, adverse effects are few[23].

Ezetimibe[10]
NICE recommends that ezetimibe be used as a treatment for adults with primary heterozygous-familial or non-familial hypercholesterolaemia in the following circumstances:

- Where statins are contra-indicated or not tolerated.
- In conjunction with a statin where serum TChol or LDL-C is not appropriately controlled by initial statin therapy (after appropriate dose titration or because dose titration is limited by intolerance) and when consideration is being given to changing the initial statin therapy to an alternative statin.

Fibrates[2]
NB: NICE does not recommend routinely using a fibrate for primary or secondary prevention of CVD, or for people with CKD, type 1 diabetes or type 2 diabetes[7].

The fibrates (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil) act mainly by decreasing serum triglycerides. Fibrates are first-line therapy only in those whose serum-triglyceride concentration is greater than 10 mmol/L or in those who cannot tolerate a statin. In type 2 diabetes, fenofibrate can be added to a statin for those with a serum-triglyceride concentration exceeding 2.3 mmol/L, despite six months of treatment with a statin and optimal glycaemic control.

- Current clinical guidelines recommend fibrates as the treatment of choice for severe isolated hypertriglyceridaemia (triglycerides (TGs) >10 mmol/L), but where this co-exists with hypercholesterolaemia (ie in mixed hyperlipidaemia), LDL reduction remains the priority and thus statins tend to remain first-line[3].
- They are uncommonly used in primary CVD prevention and for most other dyslipidaemias, fibrates have been superseded by statins [1].
- They act in the liver to reduce cholesterol synthesis, reduce secretion of very low-density lipoproteins (VLDLs) and increase the removal of VLDLs from the blood, consequently lowering plasma TGs (by 30-50%) and, to a lesser extent, plasma cholesterol (TChol and LDL reduction of 0-30%). They increase the plasma HDL (by 2-20%) by increasing apoA-I and apoA-II gene transcription.
- Evidence of efficacy in treating cardiovascular risk and of safety is less substantial than for statins: trials showed significant lipid-lowering but this did not necessarily translate into significant clinical gains.

Contra-indications
Hypoalbuminaemia, gallbladder disease, nephrotic syndrome, and photosensitivity to fibrates.
Cautions
As with statins, myotoxicity is the most important adverse effect of this class of drugs. Risk is increased by:
- Concomitant treatment with statins (CK levels >10 x ULN occur in about 1 in 1,000 individuals on combination therapy).
- Concomitant treatment with ciclosporin.
- Renal insufficiency (check U&Es prior to commencing treatment).
- Older age.
- Female sex.

Side-effects
These include:
- Myopathy and rhabdomyolysis - risk is increased if impaired renal function.
- Gastrointestinal side-effects - more common.
- Hypersensitivity reaction (urticaria, pruritus, photosensitive rash).

Starting a fibrate
Drug choice
NICE does not recommend any particular fibrate for use in CVD prevention in those intolerant of a statin. NICE Clinical Knowledge Summaries (CKS) suggest the use of bezafibrate and fenofibrate in preference to gemfibrozil (based on risk of drug interactions and expense) and ciprofibrate (based on difficulty of titration). However, there is inadequate evidence to choose between them based on efficacy.

Combination treatment
Combination treatment is no longer advocated. The NICE Guideline Development Group has concluded that supportive evidence for the benefits of adding a fibrate is lacking and is outweighed by the risks of myopathy and rhabdomyolysis [7].

Monitoring[2]
- Check U&Es prior to treatment, as renal insufficiency increases the risk of myotoxicity. Adjust the dose if there is evidence of renal insufficiency. Routine ongoing monitoring of creatinine levels, etc, is not required [24].
- Discontinue the fibrate if serum aminotransferases are three or more times the upper limit of normal.
- Check CK level only if myopathy or rhabdomyolysis is suspected: stop treatment if the CK level is five times the upper limit of normal or more.

Additional lipid-regulating drugs
Other lipid-regulating drugs are unlikely to be initiated in primary care but may be used on occasion by secondary care lipid clinics. They include:
- Colestyramine and colestipol.
- Nicotinic acid and acipimox.
- Omega-3 fish oils.

NB: NICE does not recommend using any of these medications for primary or secondary prevention of CVD, or for people with CKD, type 1 diabetes or type 2 diabetes [7].

Further reading & references
- Cardiovascular risk assessment and lipid modification; NICE Quality Standard, September 2015
- Ezetimibe for treating primary heterogous-familial and non-familial hypercholesterolaemia; NICE Technology Appraisal Guidance, February 2016
- Report of the Joint British Societies for the Prevention of Cardiovascular Disease; JBS3, 2014
- British National Formulary (BNF); NICE Evidence Services (UK access only)
- 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias; European Society of Cardiology (2016)
- Byrne P et al; Statins for the primary prevention of cardiovascular disease: an overview of systematic reviews BMJ Open 2019;9(4)
- Lipid modification - CVD prevention; NICE CKS, October 2015 (UK access only)

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