Lipid-regulating drugs (Including statins)

What are lipid-regulating drugs?

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. [1] [2]

Determining the absolute risk reduction, and therefore estimating the magnitude of benefit of treatment, requires calculating the baseline cardiovascular risk for that individual. In short, people with a high baseline cardiovascular risk are more likely to benefit from lipid-lowering therapy, whereas those with a low risk are less likely to see any benefits.

Causes of dyslipidaemia

See the separate Hyperlipidaemia article.

Prevention of cardiovascular disease

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

Types of lipid-regulating drugs

There are several classes of lipid-regulating drugs commonly prescribed, these include:

- Statins.
- Ezetimibe.
- PCSK9 inhibitors.
- Fibrates.
- Icosapent ethyl.

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.[3]

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 relative risk reduction in primary and secondary prevention is about the same. Since the absolute risk is by definition higher in secondary prevention, the benefit of statins is greater in this scenario than in primary prevention.[4]

- 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 high-intensity statins is initiated early following an acute myocardial infarction, after percutaneous coronary angiography and in acute coronary syndrome.[5]

- 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.[6]

- Statins may also reduce the risk of developing atrial fibrillation.[7]

Who should be on a statin?

National Institute for Health and Care Excellence (NICE) guidelines suggest that statins should be offered:[8]

- 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).
    - A 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 QRISK3 risk assessment tool, if lifestyle measures to reduce CVD risk have been ineffective.
    - All those aged 85 years and over by virtue of age alone, unless comorbidities, patient preference or contra-indications make this inappropriate.
    - All adults with type 1 diabetes.
    - All adults with chronic kidney disease (CKD).[9]

During discussions with patients, the degree of risk reduction should be discussed, along with the possibility of harms and side-effects, to allow for informed decision-making. Patient decision aids, such as the one produced by NICE, may be helpful.[10]

NICE recommends using a 'systematic strategy to identify people who are likely to be at high risk' of developing CVD, and reviewing this risk on an ongoing basis for people over the age of 40 - thereby essentially advocating population screening for CVD risk. [11]

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; [12] NICE currently recommends that statins are only offered for primary prevention to people with type 2 diabetes if their 10-year cardiovascular risk is 10% or greater.

Intensity of lipid lowering therapy [3]

- Low intensity statins will produce an LDL-C reduction of 20-30%.
- Medium intensity statins will produce an LDL-C reduction of 31-40%.
- High intensity statins will produce an LDL-C reduction above 40%.

High-intensity:

- Atorvastatin 20 mg daily (43% reduction in LDL cholesterol); 40 mg (49%); 80 mg (55%).
- Rosuvastatin 10 mg (43%); 20 mg (48%); 40 mg (53%).
- Simvastatin 80 mg (42%):
    - Simvastatin 80 mg is not recommended due to an increased risk of myopathy.
    - Simvastatin 80 mg should be considered only 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.
- Atorvastatin with ezetimibe 10 mg: 10 mg (52%); 20 mg (54%); 40 mg (57%); 80 mg (61%).

Medium-intensity:

- Atorvastatin 10 mg (37%).

- Fluvastatin 80 mg (33%).
- Rosuvastatin 5 mg (38%).
- Simvastatin 20 mg (32%); 40 mg (37%).

Low-intensity:

- Fluvastatin 20 mg (21%); 40 mg (27%).
- Pravastatin 10 mg (20%); 20 mg (24%); 40 mg (29%).
- Simvastatin 10 mg (27%).

Baseline tests before starting lipid-modifying therapy[13]

Perform the following baseline blood tests to ensure that lipid-modification treatment is suitable for the person:

- Creatine kinase (CK): ask the person if they have persistent generalised unexplained muscle pain (whether associated with previous lipid-lowering therapy or not). If present, measure CK level:
    - If the CK level is raised but is less than five times the upper limit of normal, start lipid-lowering treatment.
    - If the CK level is five or more times the upper limit of normal, re-measure after 7 days. If levels are still five times the upper limit of normal, seek specialist advice (for example, from a lipid clinic).
    - Do not measure CK in asymptomatic people being considered for statin treatment.
- Liver function tests (alanine aminotransferase or aspartate aminotransferase):
    - If these results are abnormal, perform further investigations to determine the cause of the abnormal test results (eg, non-alcoholic fatty liver disease).
    - Do not routinely exclude from treatment people who have liver enzymes that are elevated but are less than three times the upper limit of normal.

- Renal function (including estimated glomerular filtration rate):
    - Chronic kidney disease does not preclude the use of a lipid-lowering drug.
    - However, specific doses are recommended depending on the stage of CKD.
- HbA1c: to diagnose diabetes mellitus.
- Thyroid stimulating hormone:
    - Hypothyroidism (primary or secondary) is a recognised cause of dyslipidaemia.
    - Untreated hypothyroidism increases the risk of statin-induced myopathy.

Side-effects [3]

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

Muscle effects [4] [14]

- The most important adverse effect of these drugs is myalgia characterised by muscle and tendon pain, stiffness, muscle weakness and cramping. This affects 10-15% of patients taking statins in observational trials. However, these symptoms are common in the general population, especially with increasing age, and recent research suggests that, in many cases, these may not be directly attributable to statins. In randomised controlled trials, in which patients are blind to whether they are taking statin or placebo, there is little or no increase in muscle symptoms between statin and placebo groups. [15]
- This has also been investigated at the individual patient level: the StatinWISE trial investigated the effect of statins on muscle symptoms in people who had stopped, or were considering stopping, statins due to muscle symptoms. Participants were given atorvastatin, then placebo, in sequence and were blind to which they were taking; there was no difference in self-reported muscle symptoms when taking atorvastatin, compared to placebo. [16]

- Statin-induced myopathy includes a spectrum from asymptomatic increase in serum creatine kinase (CK) to myalgia, myositis and, most seriously, rhabdomyolysis. Rhabdomyolysis is rare (0.1-0.3 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.
- The 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. [17]

- NICE recommends if unexplained muscle symptoms (such as pain, tenderness, or weakness) develop:[13]
    - Check creatine kinase (CK) levels.
    - Stop statin treatment immediately if muscle symptoms are intolerable or if CK is five or more times the upper limit of normal.
    - If muscle pain develops but statin treatment was previously tolerated for more than 3 months, explore other possible causes of myalgia and raised CK, such as vigorous physical activity, hypothyroidism, infection, recent trauma, and drug or alcohol misuse.
    - If other adverse effects are reported, discuss the following possible strategies with the person:
        - Stopping statin treatment and trying again when the symptoms have resolved to check if the symptoms are related to statin use, or
        - Changing to an alternative high-intensity statin or ezetimibe, or
        - Referral to a specialist with expertise in FH for consideration of treatment with a bile acid sequestrant (resin) or a fibrate.

Hepatotoxicity

This is 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. This risk is relatively small, with new-onset diabetes attributable to statins occurring in approximately 1 in 200 people treated with statins for five years.[18] 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.[19]

Targets

Current NICE guidance does not recommend an absolute lipid target value, but does recommend targeting a 40% reduction in non-HDL cholesterol, or greater, after three months of treatment with statins.[8]

Initial treatment for primary prevention should be with atorvastatin 20 mg. If a 40% or greater reduction in non-HDL cholesterol is not achieved, medication, diet and lifestyle adherence should be explored with the patient. If these have been adequately addressed, the atorvastatin dose can be increased.

Initial treatment for secondary prevention should be atorvastatin 80 mg, unless there are potential drug interactions, a high risk of adverse effects, or the patient prefers otherwise, in which case a lower starting dose can be used.

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.[20]

Initiating and monitoring treatment

Choosing a statin[8]

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[8]

- Check lipids, LFTs, HbA1c, renal function, and TSH prior to starting treatment (if not already done). Fasting samples for lipids are not required.

- If LFTs are abnormal, perform further testing to establish the cause (eg, non-alcoholic fatty liver disease). Liver enzymes that are up to three times the upper limit of normal do not preclude statin initiation.
- Exclude any secondary causes of hypercholesterolaemia (eg, excess alcohol, 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 the upper limit of normal, do not prescribe a statin. If CK is raised but <5 times the upper limit of normal, prescribe a statin, but in the lower-dose range.
- Measure CK if a patient reports muscle pain, tenderness, or weakness whilst taking statins. .
- *Do not* routinely monitor CK unless clinically indicated:[21]

Where CK is:
Normal: this is myalgia. Continue a statin where symptoms are tolerable and not progressive. If intolerable, offer the patient the options of stopping the statin and re-starting when symptoms improve, reducing the dose, or changing to a lower-intensity statin.
Raised but <10 x upper limit of normal (ULN): this is myositis. NICE recommends stopping statin therapy if the CK is **five times the upper limit of normal or greater**. If below this level, statins can be continued if symptoms are tolerable or stopped and consider alternatives if not. Where muscular symptoms or raised CK continue to persist despite statin cessation, 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.[22]

- Repeat LFTs after three months of treatment, at a year, and if there are any signs or symptoms of hepatotoxicity. 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[8] [23]

- 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.[24]

Patient advice[23]

Good patient information and education improve adherence. 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.[10]
- These drugs need to be taken as ongoing medications. Stopping taking 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[13]

NICE recommends considering the use of lipid-modifying drugs in children with familial hypercholesterolaemia by the age of 10 years. 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.[25]

Editor's note

Dr Krishna Vakharia, 13th September 2024

Evinacumab for treating homozygous familial hypercholesterolaemia in people 12 years and over [26]

NICE is recommending evinacumab alongside diet and other LDL-C lowering therapies as an option for treating homozygous familial hypercholesterolaemia in people 12 years and over.

Evinacumab is a human monoclonal antibody that binds to and blocks the angiopoeitin-like 3 protein (ANGPTL3) to prevent its inhibition of lipoprotein and endothelial lipase, this then lowers triglycerides and cholesterol.

Clinical evidence suggests that evinacumab can lower LDL-C levels when statins and other lipid-lowering therapies have not reduced them enough.

Evinacumab is a recombinant human monoclonal antibody that binds to and blocks the angiopoeitin-like 3 protein (ANGPTL3) to prevent its inhibition of lipoprotein and endothelial lipase, thereby lowering triglycerides and cholesterol.

Ezetimibe [23]

NICE recommends that ezetimibe be used as a treatment for adults with primary heterozygous-familial or non-familial hypercholesterolaemia in the following circumstances: [27]

- 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.

If ezetimbe monotherapy does not reduce LDL-C enough, bempedoic acid can be added. [28]

PCSK9 inhibitors

These are a new class of medicines which act on proprotein convertase subtilisin/kexin type 9 (PCSK9), an important regulator of cholesterol mechanism. There are currently two monoclonal antibodies available, alirocumab and evolocumab, which reduce PCSK9 activity, and a small interfering RNA (siRNA) drug, inclisiran, which inhibits the hepatic translation of PCSK9.

NICE has approved the use of alirocumab and evolocumab in the following situations only:[29] [30]

- Secondary prevention of CVD in non-familial hypercholesterolaemia or dyslipidaemia, where, despite maximal lipid-lowering treatment, LDL-C concentration is persistently above 4.0 mmol/L (or above 3.5 mmol/L in people at very high CVD risk).
- Primary or secondary prevention in heterozygous familial hypercholesterolaemia, where despite maximal lipid-lowering treatment, LDL-C concentration is persistently above 5.0 mmol/L in primary prevention, or above 3.5 mmol/L in secondary prevention.

NICE has approved inclisiran for secondary prevention of CVD only, and only where LDL-C concentrations are persistently 2.6 mmol/L or more, despite maximum-tolerated lipid-lowering therapy (ie maximum-tolerated statins, with or without other lipid-lowering therapies, or other lipid-lowering therapies where statins are not tolerated or are contra-indicated).[31]

Fibrates[3]

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.[8]

The fibrates (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil) act mainly by decreasing serum triglycerides.

- 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.

Fibrates should generally not be initiated in primary care, but may be considered by secondary care services.

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 rhabdomyolyis - risk is increased if impaired renal function.
- Gastrointestinal side-effects - more common.
- Hypersensitivity reaction (urticaria, pruritus, photosensitive rash).

Icosapent ethyl[32]

Icosapent ethyl is a purified preparation of the omega-3 fatty acid eicosapentaenoic acid. NICE has recommended it as an option for **secondary prevention of CVD** in people who: are at high risk of CVD, **and** are taking statins, **and** have raised fasting triglycerides (1.7 mmol/L or above), **and** have LDL-C levels between 1.04 mmol/L and 2.60 mmol/L.

Icosapent ethyl is also licensed for primary prevention in people who have diabetes and one other cardiovascular risk factor. **NICE has not recommended it for primary prevention** but it can be used as secondary prevention in people with diabetes and established cardiovascular disease.

Clinical trial evidence suggests that icosapent ethyl reduced the risk of cardiovascular events in people with raised fasting triglycerides (1.7 mmol/L or above) who are taking statins compared to placebo. The trial only included people with LDL-C levels above 1.04 mmol/L and below or equal to 2.60 mmol/L.

People must be taking a statin to have icosapent ethyl. People who cannot have statins are not covered by icosapent ethyl's marketing authorisation, so NICE has not made any recommendations in this area.

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.[8]

Further reading

- Su X, Kong Y, Peng D; Evidence for changing lipid management strategy to focus on non-high density lipoprotein cholesterol. Lipids Health Dis. 2019 Jun 7;18(1):134. doi: 10.1186/s12944-019-1080-x.
- Zodda D, Giammona R, Schifilliti S; Treatment Strategy for Dyslipidemia in Cardiovascular Disease Prevention: Focus on Old and New Drugs. Pharmacy (Basel). 2018 Jan 21;6(1). pii: pharmacy6010010. doi: 10.3390/pharmacy6010010.
- Cardiovascular risk assessment and lipid modification; NICE Quality standard, May 2023

Last updated by: Dr Colin Tidy, MRCGP 15/06/2023	
Peer reviewed by: Dr Krishna Vakharia, MRCGP 15/06/2023	**Next review date:** 13/06/2028