Higher blood levels of LDL cholesterol mean higher rates of coronary heart disease, for different populations and at various concentrations of LDL cholesterol. For example, LDL cholesterol concentrations typically exceed 13mmol/L in individuals with homozygous familial hypercholesterolaemia and they can develop coronary events by their 20s or 30s. In people with heterozygous hypercholesterolaemia, LDL cholesterol can be above 8mmol/L and coronary events occur in the mid-50s.

Since the launch of the statins in the mid-1990s, and in particular the introduction of the government’s National Service Framework for Coronary Heart Disease in 2000, lipid-lowering has been an integral and very successful component of pharmacological strategies to reduce cardiovascular risk. Between 1961 and 2012, the proportion of deaths in the UK caused by cardiovascular disease fell from 50% to 28%. Many factors have contributed – less smoking, treatment for hypertension and diabetes, antiplatelet therapy, increased physical activity – but, with about 80% of people with atherosclerotic disease now prescribed a statin and nearly 68 million prescriptions dispensed in 2016 in England alone, these drugs are likely to have played a big part. The statins are more effective than any of the cholesterol-lowering drugs preceding them: intensive statin therapy can halve LDL cholesterol levels by up to 2mmol/L (about half the population have a level of about 4mmol/L).

Randomised controlled trials have shown that each 1mmol/L reduction in LDL cholesterol reduces the rate of major vascular events by about a quarter annually from the second year of treatment. A 2mmol/L reduction in LDL cholesterol for five years in 10,000 patients would prevent major vascular events in an estimated 1000 patients with pre-existing...
vascular disease (as secondary prevention) and in 500 people at increased risk as primary prevention.¹

**Beyond statins**

Not all statins were created equal. Pravastatin and fluvastatin offer a relatively modest reduction in LDL cholesterol, inferior to that of simvastatin and well below the high-potency atorvastatin and rosuvastatin (see Figure 1).⁸ For some time, when high-potency statins were available only as branded products and were priced accordingly, management guidance recommended simvastatin – first at a ‘standard’ dosage (20–40mg daily) then at a high dosage (80mg daily). Following the expiry of patent protection for Lipitor (atorvastatin) in 2011, the tables turned: atorvastatin prescribing has been growing by 20% annually and it is now set to surpass simvastatin as the most frequently prescribed statin.⁹

So, as resources allowed, the approach to lipid-lowering therapy has become more aggressive. NICE now recommends initiating atorvastatin at a dosage of 80mg daily for secondary prevention of cardiovascular disease, provided the risk of drug interactions and adverse effects is acceptable, and subject to patient preference.¹⁰ (The recommended dosage for primary prevention is 20mg daily.) The aim is to reduce non-HDL cholesterol by 40%. The strategy is similar for people with familial hypercholesterolaemia, with the aim of reducing LDL cholesterol by 50%.¹¹

Evidently, even high-intensity statins are not sufficient in some cases. There is variability between patients in the reduction of LDL cholesterol achieved² and, in clinical practice, many do not achieve the desired level.¹³ Why should statin monotherapy not deliver an adequate reduction in LDL cholesterol? Very high cholesterol levels, as may occur in people with familial hypercholesterolaemia, will still be high even after a 50% reduction. Adding ezetimibe, which exerts a complementary mechanism of action by inhibiting intestinal absorption of cholesterol, increases the proportion of patients achieving the target LDL cholesterol reduction but, even with this strategy, the reduction in LDL cholesterol is less than hoped for in about 20% of patients.¹⁴

**Adverse effects and adherence**

Some people can’t take statins, and some people won’t. The tolerability of statins became a controversial topic when, in 2014, NICE recommended atorvastatin for primary prevention in people with a ≥10% 10-year risk of developing cardiovascular disease.¹⁰ The balance of risks and benefits was undisputed for secondary prevention but a review of clinical trial data concluded that it was unfavourable for primary prevention.¹⁵

This raised the profile of the adverse effects of statins, prompting a detailed rebuttal by advocates of wider use.¹ This response, which for the moment is the last and most comprehensive word on the subject, concluded that there is convincing evidence only that statins increase the risk of myopathy (by five cases per 10,000 patients treated for five years), diabetes (by 50–100 cases) and haemorrhagic stroke (by 5–10 cases). The absolute excess of adverse events associated with statins is about 1%–2%, it added, and there is “good evidence” that they do not cause symptomatic effects such as muscle pain and weakness (known as “statin intolerance”). How well the safety findings of clinical trials in populations selected for lower morbidity translate to clinical practice is a moot point and a different analysis put the risk of adverse effects of all severities at 18%.¹⁵ In the USA, the National Lipid Association Statin Safety Task Force concluded:¹⁶ “The clinician should acknowledge that statin intolerance is a real phenomenon, manifesting mostly as an array of muscle-related symptoms that include aching, stiffness, proximal motor weakness, fatigue, and back pain. Estimates of the frequency of muscle symptoms verifiably related to statin use range from 1% to 10%. Severe myopathy with objective weakness and/or markedly elevated muscle enzymes is rare. Reliable research designs are only beginning to address the actual frequency of statin muscle intolerance in populations.”¹⁶

However, investigators from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) recently implied that statin intolerance is less than real; their analysis of adverse events (AE) reported in the trial showed “an excess rate of muscle-related AE reports only when patients and their doctors were aware that statin therapy was being used and not when its use was blinded... most AEs associated with statins are not causally related to use of the drug...”¹⁷

The concept of statin intolerance is now established in the public consciousness and in regulatory decision-making...
The enzyme PCSK9 binds to LDL receptors and promotes their degradation by hepatocytes, which has the effect of raising LDL cholesterol. Gene mutations that increase PCSK9 function occur in some individuals with familial hypercholesterolaemia; conversely, mutations that decrease PCSK9 function are associated with low levels of LDL cholesterol. PCSK9 inhibitors prevent the formation of the enzyme-receptor complex, preserving LDL receptors and thereby increasing hepatic LDL uptake from the circulation. They also increase levels of favourable HDL cholesterol in the circulation.

Two PCSK9 inhibitors were introduced in the UK in 2016 as adjuncts in lipid-lowering therapy. Evolocumab (Repatha) and alirocumab (Praluent) are monoclonal antibodies that bind to PCSK9, producing a profound reduction in circulating LDL cholesterol (see Figure 2). Both are licensed for use in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet. They can be used in combination with a statin (alone or with other lipid-lowering agents) in patients who cannot achieve the required reduction in LDL cholesterol at the maximum tolerated dose of a statin; or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated. Evolocumab is also licensed for use, in combination with other lipid-lowering agents, in adults and young people over 12 years with homozygous familial hypercholesterolaemia.

**Dosage and administration**

Both PCSK9 inhibitors are administered by subcutaneous injection but the dose regimens for primary hypercholesterolaemia are slightly different. The initial dosage of evolocumab is 140mg every two weeks or 420mg monthly (the dosages are clinically equivalent, see Figure 2). Alirocumab is usually initiated at a dosage of 75mg every two weeks but a higher dosage of 150mg every two weeks (or 300mg every month) can be used if a greater initial reduction in LDL cholesterol is required. For patients with homozygous familial hypercholesterolaemia, the initial dosage of evolocumab is 420mg monthly, increased after 12 weeks if necessary to 420mg every two weeks.

Both PCSK9 inhibitors have been marketed in pre-filled single-use pens. A 300mg dose of alirocumab requires the use of two pens; the evolocumab SureClick pen contains 140mg and three pens are needed for the 420mg dose (or a 420mg cartridge is also available).

No dose adjustment is recommended for older people (though experience in the over-75s is limited) or in patients with mild or moderate renal impairment or mild hepatic impairment. Evolocumab should be monitored closely in patients with moderate hepatic impairment because total exposure is lower and the effect on LDL cholesterol levels may be reduced. There is little experience with either drug in patients with severe renal or hepatic impairment.

**Clinical use**

NICE has recommended evolocumab and alirocumab as options for treating primary hypercholesterolaemia or mixed dyslipidaemia when LDL cholesterol is persistently above specified thresholds (see Table 1) after maximal tolerated lipid-lowering therapy. This is conditional on price discounting via confidential
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Figure 3. Mean % change in LDL cholesterol from baseline, during long-term treatment with alirocumab when added to statin±ezetimibe therapy in patients with heterozygous familial hypercholesterolaemia.

Adverse effects

A meta-analysis of 25 trials of evolocumab or alirocumab involving a total of 12,200 patients found that the overall rate of treatment-emergent adverse events was similar to that reported with ezetimibe and placebo over 12–52 weeks (50%–70%) and rates of specific adverse events were not statistically significantly different. The most frequently reported events were musculoskeletal disorders (10%–17% of patients), including back pain, arthralgia, muscle spasms and myalgia, nasopharyngitis and gastrointestinal disorders. Injection-site reactions were reported by about 2% of patients using evolocumab (vs 2% with placebo) and about 6% with alirocumab (vs 4% with placebo). Prescribing information for alirocumab states that most injection site reactions were transient and of mild intensity, resulting in discontinuation in 0.2% of patients (vs 0.3% in controls).

Overall, the frequency of discontinuation due to adverse events in clinical trials was 1.9% with evolocumab (vs 2.3% with controls); in the case of alirocumab, it was 5.3% vs 5.1% with placebo and 8.8% vs 9.7% with ezetimibe.

Summary

Reducing LDL cholesterol is crucial to lowering the risk of cardiovascular events and for most people, lifestyle change, statins and ezetimibe are effective. However, about one in 12 patients with non-familial hypercholesterolaemia, and one in seven of those with familial hypercholesterolaemia, do not reach the desired reduction in LDL cholesterol with this approach. NICE has recommended a new treatment step with the addition of evolocumab or alirocumab, both of which offer a further substantial reduction in LDL cholesterol and, on the basis of current evidence, good tolerability. The additional cost to the NHS is being withheld but, on the basis of the standard price of each agent, it is likely to be high.

References


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