Properties and use of statins in cardiovascular disease

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Steve Chaplin and Professor Paul Collinson provide an overview of the properties of statins and how they compare in lowering cholesterol levels and the prevention of cardiovascular disease.

KEY POINTS

- there are currently five statins available: atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin; simvastatin is also available combined with ezetimibe
- they are all indicated for use in hypercholesterolaemia; other indications include primary and secondary prevention of cardiovascular events
- high-intensity statins include 80mg simvastatin, atorvastatin and rosuvastatin
- caution is needed when prescribing in patients with a history of liver disease or a high alcohol intake; they should be avoided in active liver disease, elevated transaminases and acute porphyria
- liver enzymes should be measured before starting treatment and repeated within 3 months and at 12 months
- muscle toxicity is more common with high-intensity statins and when given with a fibrate or nicotinic acid; patients should be advised to report unexplained muscle pain, tenderness or weakness
- current guidelines recommend simvastatin as the agent of first choice; this may change now that atorvastatin is available generically

The *BNF* lists five statins (see Table 1). They are the most effective treatment for lowering LDL-cholesterol and reducing cardiovascular events and total mortality irrespective of baseline cholesterol levels. They are less effective than the fibrates at reducing triglycerides.

The licensed indications vary: for example, the two newest, atorvastatin and rosuvastatin (Crestor), are not specifically licensed for secondary prevention (see Table 1).

The main distinction the *BNF* makes between them is in its definition of a high-intensity statin as one that achieves a greater reduction in LDL-cholesterol than simvastatin 40mg daily, such as simvastatin 80mg daily, atorvastatin and rosuvastatin. NICE recommends a high-intensity statin for secondary prevention of cardiovascular events but not routinely for primary prevention. However, the *BNF* suggests considering an alternative statin if muscle toxicity occurs during treatment (see below), implying that tolerability may vary.

Although statins have a common toxicity profile, each is also associated with specific rare adverse effects.

Statins are routinely combined with other interventions. For the reduction of cardiovascular risk, they should be part of a package of care that includes diet, lifestyle change, low-dose aspirin, lowering raised blood pressure and the management of diabetes. High-intensity statins are also indicated for patients with acute coronary syndrome.

Simvastatin is available in combination with ezetimibe (Inegy), which inhibits intestinal absorption of cholesterol, for the treatment of hypercholesterolaemia. A statin may be combined with other lipid-lowering agents in the treatment of severe hyperlipidaemia (ezetimibe, colestyramine) and hyperlipidaemias with very high LDL-cholesterol and/or triglyceride levels (fenofibrate, nicotinic acid). Such combinations are associated with an increased risk of adverse effects and require specialist supervision and monitoring.

Statin	HCA	1^{y} CVD	2^{y} CVD	Adult daily dose	Cost per 28 days
Atorvastatin	✓[a]	✓	-	10–80mg	£1.35–£4.15
Fluvastatin	✓	-	✓[c]	20–80mg daily	£3.36–£6.80 (£19.20 – 80mg m/r od)
Pravastatin	✓[ab]	✓	✓	10–40mg	£1.36–£2.37
Rosuvastatin	✓[a]	✓	-	5–40mg	£18.03–£29.69
Simvastatin	✓[a]	✓	✓	10–80mg	67p–£1.67
Simvastatin/ezetimibe	✓[a]	-	-	20/10–80/10mg	£33.42–£41.21

CVD = cardiovascular disease: 1^{y} = primary prevention, 2^{y} = secondary prevention
HCA = primary and mixed hypercholesterolaemia
[a]includes familial hypercholesterolaemia
[b]includes post-transplant hyperlipidaemia
[c]secondary prevention of major adverse cardiac events in adults with coronary heart disease after percutaneous coronary interventions

Table 1. Licensed indications, doses and costs (*MIMS*, January 2013) of statins

Statins may be prescribed by specialists to treat hypercholesterolaemia in children but none are licensed for children younger than 8–10 years (depending on the specific agent) due to lack of clinical experience.

Caution is needed when prescribing a statin for patients with a history of liver disease or a high alcohol intake; they should be avoided in patients with active liver disease, persistent unexplained elevated transaminases or acute porphyria. Liver enzymes should be measured before starting treatment and after 3 and 12 months. Treatment should be discontinued if transaminases are raised above three times the normal upper limit.

It can be difficult to correct hypothyroidism during treatment with a statin and uncorrected hypothyroidism increases the risk of myositis. Thyroid function should therefore be checked and corrected before starting treatment.

Adverse effects

Statins have been associated with a range of adverse effects involving most organ systems, reflecting long experience of widespread use. Muscle toxicity – myalgia, myopathy, myositis and rhabdomyolysis – is a class effect but is more common with high-intensity statins and when given with a fibrate (the combination with gemfibrozil is contraindicated) or nicotinic acid.

The risk is also increased by drugs that increase statin levels such as the macrolide antibiotics, fusidic acid, some antifungals, protease inhibitors and ciclosporin. Other risk factors include a family history of muscle disorders, previous muscle toxicity, hypothyroidism (see above), high alcohol intake, renal impairment and older age.

Reduced doses are recommended for patients with at least moderate renal impairment (except for atorvastatin) and rosuvastatin should be avoided in patients with severe renal impairment. The initial dose of rosuvastatin should be 5mg daily in elderly patients. Its bioavailability is increased in patients of Asian origin, who should also begin treatment at 5mg daily and not exceed a daily dose of 20mg.

Patients should be advised to report unexplained muscle pain, tenderness or weakness while taking a statin. The *BNF* states that muscle toxicity truly attributable to statins is rare and routine monitoring of creatine kinase is unnecessary in asymptomatic patients. Other causes, *eg* strenuous exercise, infection, recent trauma, should be excluded if muscle symptoms or raised creatine kinase occur during treatment.

If a statin is the cause, the criteria for discontinuing treatment are severe muscle symptoms or creatine kinase raised above five times the normal upper limit. If symptoms resolve and creatine

	No. scrips (000s)	NIC (£000)	NIC per scrip (£)
Atorvastatin	11 358	310 863	27.37
Fluvastatin	177	1 587	8.99
Pravastatin	2 494	6 412	2.57
Rosuvastatin	2 136	53 650	25.11
Simvastatin	41 164	61 191	1.49
Simvastatin/ezetimibe	126	6 240	49.56

Table 2. GP prescriptions and net ingredient cost (NIC) for statins in England, 2011

kinase becomes normal, treatment should be reintroduced at a lower dose or with a different statin. A statin should not be discontinued if creatine kinase is slightly elevated and the patient is asymptomatic.

Statins should not be prescribed for patients at increased risk of muscle toxicity if creatine kinase is more than five times the normal upper limit. However, creatine kinase levels may be high in patients with a physical occupation or after exercise; specialist advice should then be sought.

Statins may affect fetal development and are contraindicated during pregnancy; contraception should continue for one month after stopping treatment.

In 2011, GPs in England wrote a total of 57 million prescriptions for statins at a total cost of approximately £440 million. Simvastatin accounted for over 70 per cent of scrips but only 14 per cent of costs. The reverse was true for atorvastatin, which accounted for 20 per cent of scrips and 70 per cent of costs; it is now available generically.

Prescribing statistics for statins are summarised in Table 2.

Declaration of interests

Steve Chaplin has undertaken paid writing work for several pharmaceutical companies.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics

Place in therapy

Before prescribing a statin, the first and most important distinction to make is between treatment for primary and secondary prevention of ischaemic heart disease.

Secondary prevention (established coronary disease, peripheral vascular disease, carotid artery disease or a previous history of thrombotic stroke) is straightforward. All such patients should receive a statin unless there is an absolute contraindication.

Treatment for primary prevention is more complicated. Cholesterol values should not be used as the sole indication for treatment and a more holistic approach is required. Prior to any medication individuals should undergo risk stratification using an appropriate tool such as QRisk or the European Cardiac Society HeartScore program. Treatment with a statin should be reserved for those identified at high risk who do not respond to lifestyle modification.

Common mistakes

A common mistake is to act on a single cholesterol measurement. Although the initial measurement of cholesterol does not have to be fasting (this is a common misapprehension, only triglycerides are significantly affected by the fasting or nonfasting state), an elevated value should be confirmed by at least one and preferably two subsequent fasting values.

The time between repeats depends on the strategy to be employed. Confirmation of an elevated value can occur with repeat values within the next two to three weeks; if the effect of lifestyle interventions is to be assessed, repeat values over the next two to three months are more sensible.

The second common mistake is to fail to take into account HDL-cholesterol. Referrals for specialist advice in individuals with elevated total cholesterol due to an elevated HDL and normal LDL cholesterol are depressingly common and a waste of resources. If your local laboratory does not routinely provide you with an HDL-cholesterol, change laboratory.

Pretreatment tests

Prior to treatment a baseline set of liver function tests and creatine kinase should be performed. This prevents the embarrassment of subsequent tests done for monitoring that are found to be abnormal and do not change on discontinuation of the statin. It also allows for ethnic variation in creatine kinase values – higher in Asians and Afro-Caribbeans.

Normal thyroid function should be established and obvious causes of secondary hypercholesterolaemia excluded.

Statin treatment

Once treatment is to be initiated the current guidelines recommend simvastatin as the first agent, although this may change now atorvastatin has come off patent. Although a 40mg dose is recommended, a more prudent strategy is to start on a lower dose and progressively build up: this will result in improved adherence and a lower incidence of side-effects.

A common but often overlooked cause of myalgia on statin therapy is vitamin D deficiency. This may be subclinical in caucasian patients but is both highly prevalent and often severe in Asians, especially Asian females. As it is readily prevented by oral vitamin D_3 supplementation, vitamin D deficiency should be actively sought.

The individual statins may be broadly classified into those that are predominately lipid soluble (fluvastatin, simvastatin and atorvastatin) and those that are more water soluble (pravastatin and rosuvastatin).

In patients who develop side-effects it is important to exclude any underlying pathology (especially vitamin D deficiency), then consider switching from a higher dose of a weaker statin (40mg simvastatin) to a smaller dose of a more potent one (10mg atorvastatin), which may solve the problem.

If this is ineffective, switching from a lipid-soluble to a water-soluble statin, slowly introduced and with the dose built up gradually, may resolve the problem.

Declaration of interests
None to declare.

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