

The statins: a drug class to celebrate

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Part 1 of this article provides an overview of the statins – safe and effective lipid-lowering drugs for preventing major cardiovascular events. Part 2 will look at the trials that have provided the evidence base for their use.

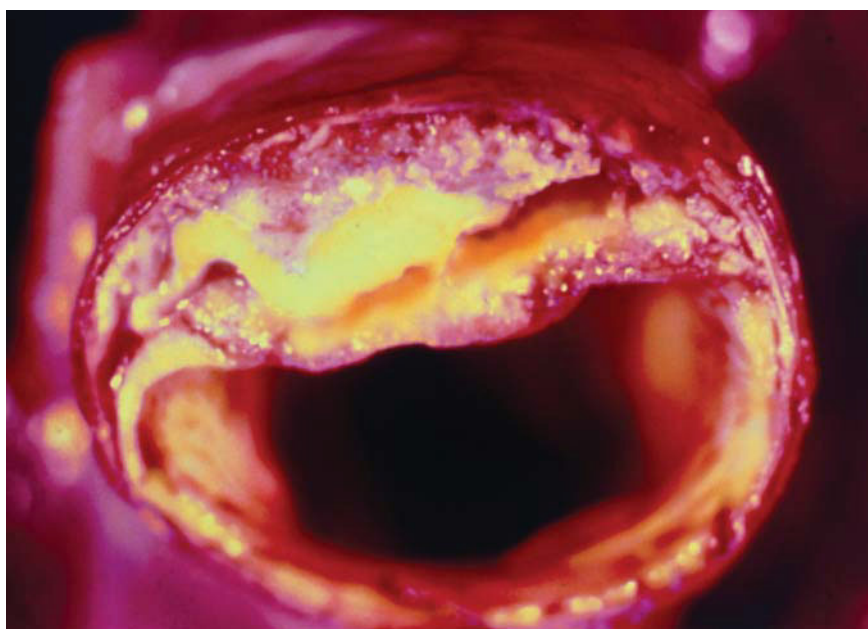


Figure 1. Atherosclerotic plaque inside artery. The main benefit of the statins is to reduce the clinical consequences of atherosclerosis (©BSIP VEM/Science Photo Library)

Pharmacological treatment of dyslipidaemia has progressed enormously in the past two decades, such that it has become one of the most successful of all therapeutic strategies. The comprehensive data available from randomised controlled trials (RCTs) allow the clinician to make informed, evidence-based treatment decisions in many groups of patients. Importantly, benefits go beyond the surrogates of changes in plasma lipid and lipoprotein concentrations to the real target, which is the reduction of the clinical consequences of atherosclerotic vascular disease (Figure 1).

These landmark developments are largely a result of the introduction of the statins in 1985. These drugs proved to be highly effective in lowering plasma low-density lipoprotein (LDL)-cholesterol and, in addition, safe and well tolerated. The availability of the statins enabled, for the first time, definitive trials to be undertaken to test the potential of LDL-lowering for the reduction of vascular events and mortality.

The importance of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in cholesterol homeostasis was becoming established in the 1960s and 70s and prompted a search for inhibitors of the enzyme. It was the pioneering work of Akira Endo that produced the prototype statin, compactin, isolated from the culture broth of



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Penicillium citrinum. This compound, which was not developed for general clinical use, proved to be effective in reducing LDL-cholesterol in patients with hypercholesterolaemia and mixed hyperlipidaemia, and led to the development of the statins that are in use today.¹

MECHANISM OF ACTION

Statins are specific, competitive inhibitors of hepatic HMG-CoA reductase, which catalyses the first committed step, also an important regulatory step, in cholesterol synthesis, namely the conversion of HMG-CoA to mevalonate. They are extremely potent compounds, with inhibitory constants of around 10^{-9} molar. Inhibition (approximately 40 per cent *in vivo*) of cholesterol synthesis induces a series of reactions to restore cellular cholesterol homeostasis involving a family of regulatory proteins, sterol regulatory element binding proteins (SREBPs).

These proteins control the transcription of key enzymes and proteins in cholesterol metabolism, including the LDL receptor. Reduced intracellular cholesterol promotes cleavage of the membrane-bound SREBP, which releases the active transcription factor; this translocates to the nucleus, enhancing the transcription of the LDL receptor.²

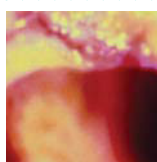
The liver is the major organ for cholesterol synthesis and for LDL catabolism; hepatic LDL activity is a major determinant of plasma LDL-cholesterol and apoprotein B concentrations. Kinetic studies *in vivo* have demonstrated that statins stimulate catabolism of LDL and other lipoproteins of the very low-density lipoprotein cascade such as remnant particles.^{3,4}

PHARMACOLOGY

The first statins, lovastatin, simvastatin and pravastatin, were derived from fungal metabolites. Subsequently synthetic statins, fluvastatin, atorvastatin, rosuvastatin and pitavastatin (available in Japan) have been introduced. They have in

common a dihydroxy heptenoic side-chain responsible for binding to the active site of HMG-CoA; this has been demonstrated by X-ray crystallography.⁵

Much has been made of the potential differences between the metabolism of the various statins and what makes the perfect statin, but the relative clinical impact of many of these factors is probably low apart from that of potential drug interactions largely, but not fully, determined by differing metabolism through the cytochrome p450 system.^{6,7}



Statins are the most effective drugs for lowering total and LDL-cholesterol levels, resulting in reductions of 30–60 per cent, and are first-line therapy in most patients

Some statins are administered as lactones (eg lovastatin and simvastatin), which are metabolised to the open acid form in the liver, while others (eg atorvastatin, fluvastatin, pravastatin and rosuvastatin) are administered as salts of their hydroxy acids. All statins are rapidly absorbed and reach peak concentrations at approximately four to five hours. The degree of absorption does vary, ranging from approximately 30–40 per cent with atorvastatin, lovastatin and pravastatin to rosuvastatin (50 per cent), simvastatin and pitavastatin (80 per cent) and fluvastatin (98 per cent).

Statins undergo extensive first-pass metabolism by the liver and therefore have low systemic bioavailability and, apart from pravastatin (46–57 per cent), are highly protein-bound (88–99.5 per cent). Most statins have a short elimination half-time (less than two hours), but the half-times of atorvastatin (11–30 hours) and rosuvastatin (19 hours) are considerably longer. Of the statins, pravastatin is the most hydrophilic compound, followed by rosuvastatin; the others are lipophilic.

The liver is the site of metabolism of most statins. Atorvastatin, lovastatin and simvastatin are metabolised through CYP 3A4 and fluvastatin is metabolised through CYP 2C9. Rosuvastatin undergoes only limited metabolism (10 per cent) through CYP 2C9 and, to a lesser extent, 2C19; 90 per cent is excreted unchanged in the faeces. Pravastatin is not metabolised through the CYP system and 60 per cent is excreted in the urine.^{6,7} Clearly there is potential for increased plasma levels if statin metabolism through CYP 450 enzymes is inhibited by other drugs. Of

interest, grapefruit contains inhibitors of CYP 450 3A4, so should not be consumed to excess by patients taking simvastatin, lovastatin or atorvastatin.

CLINICAL EFFICACY

Statins are the most effective drugs for lowering total and LDL-cholesterol levels, resulting in reductions of 30–60 per cent, and are first-line therapy in most patients. They are effective in polygenic hypercholesterolaemia, heterozygous familial hypercholesterolaemia, mixed lipaemia, familial combined hyperlipidaemia and type 3 dyslipidaemia.

Effects are dose dependent, independent of baseline LDL concentrations, and maximal after 3–4 weeks. Dose response is not linear; each doubling of dose results in an approximately 6 per cent further reduction. Apoprotein B concentrations tend to be reduced to a similar degree to LDL. Effects on plasma triglycerides vary depending on baseline levels; with baseline triglycerides >2.8 mmol/l, similar percentage reductions are seen to those for LDL, but when baseline levels are low, effects on triglycerides are more modest.⁸ Effects

on high-density lipoprotein-cholesterol are small, usually of the order of 5–10 per cent.

Statins vary in their efficacy in reducing LDL-cholesterol concentrations as shown in head-to-head comparative studies, the most effective being atorvastatin and rosuvastatin.^{9,10} Clearly, it is important to take efficacy into account when choosing a particular drug, but there are many other factors that need to be considered: evidence of benefit on clinical endpoints and safety in long-term RCTs, co-existent drug therapy, comorbidities in the individual patient, the treatment goal considered appropriate and, increasingly, cost. This latter issue is largely determined by whether or not the particular drug is off patent.

SAFETY OF STATINS

The statins have proved to be highly effective in preventing major cardiovascular events in both primary and secondary prevention trials in a wide range of at-risk patient groups with a wide range of baseline lipid concentrations. Along with this impressive efficacy, they have proved to be generally safe and well tolerated. The reader is referred to some comprehensive reviews



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based on data from long-term RCTs and post-marketing surveillance.^{11–15}

The statins, for the first time, have enabled cholesterol and LDL-cholesterol to be lowered substantially. Furthermore, more recent trials have focused on more intensive therapy to address the possibility of further cardiovascular disease event reduction. It appears that during the course of well-conducted clinical trials, as analysed in the Cholesterol Trialists' Collaboration, which performed a meta-analysis of 14 RCTs involving over 90 000 subjects, statin therapy is not associated with an increase in non-cardiac deaths and the number of incident cancers was similar whether on statin or placebo.¹¹

Individual data sheets for the different compounds list the various side-effects, common ones being mild gastrointestinal effects, weakness, headaches, and aches and pains. Here, the most serious adverse

effects will be discussed: namely, myositis and liver function abnormalities.

Myositis

Myositis (also called myopathy) is defined as generalised muscle pain and tenderness accompanied by a more than ten-fold increased creatinine kinase concentration. Fortunately this severe side-effect, which can progress to rhabdomyolysis and renal failure, is extremely rare. It can occur with all the statins and is more frequent with higher doses, but is not clearly related to the LDL-lowering.

In a systematic review of statin safety,¹⁴ the estimated risk was 11 per 100 000 person-years. It should be noted that this figure includes cases caused by drug interactions. Even at high statin dosage, myositis is very rare as, for instance, with atorvastatin, 80mg/day, based on 49 completed trials in 12 056 patients.¹⁶ In a trial of simvastatin 80mg/day there were nine cases of myositis¹⁷ and there does appear to be a step-up in risk from 40mg/day as indicated in the data sheet.

Less information is available for rosuvastatin because some long-term RCTs are awaited. However, in a recent publication based on 5011 patients aged at least 60 years with systolic heart failure, rosuvastatin 10mg/day did not produce an excess of myositis compared to placebo.¹⁸ Although there are undoubtedly clinical problems in practice, there is no evidence from RCTs that statins cause myalgia or muscle cramps.¹⁹

Liver function abnormalities

A small percentage of statin-treated patients (again dose related) develop abnormal liver function tests, as manifest by rises in transaminases. Whether these

KEY POINTS

- Statins are highly effective in lowering plasma LDL-cholesterol and, in addition, are safe and well tolerated
- The main benefit of statin therapy is the reduction of the clinical consequences of atherosclerotic vascular disease
- Statins are specific, competitive inhibitors of hepatic HMG-CoA reductase, which catalyses the first step in cholesterol synthesis, the conversion of HMG-CoA to mevalonate
- All statins are rapidly absorbed and reach peak concentrations at approximately four to five hours
- Atorvastatin and rosuvastatin are the most effective in reducing LDL-cholesterol concentrations, although many other factors need to be considered when choosing a particular drug
- Common side-effects of statins include mild gastrointestinal effects, weakness, headaches, and aches and pains. The most serious adverse effects are myositis and liver function abnormalities

changes represent hepatotoxicity or are a result of LDL-lowering is not clear. Of interest, lipid-lowering with resins, which are not systemically absorbed, can also increase transaminases. A greater than three-fold rise is usually taken as a significant increase. There is little evidence that these changes are associated with more serious liver damage; they revert to normal on stopping or reducing drug dosage.¹⁹

In one study of atorvastatin 80mg/day in acute coronary syndrome, 2.5 per cent of patients on the drug compared to 0.6 per cent on placebo developed high transaminases.²⁰ Three of the affected atorvastatin-treated patients were hospitalised for hepatitis. This has not been reported in subsequent studies; however, it is clear that high transaminases are seen in 1–2 per cent of patients on high dose.¹⁶ There is also a slight increase with simvastatin.¹⁷

Clearly, information from long-term RCTs provides the best information on adverse effects as there is no bias as compared to spontaneous reports. Several possible adverse reactions, including sleep and mood disorders, dementias and peripheral neuropathy, have been reported spontaneously but not seen in RCTs.¹⁹

Declaration of interests

John Betteridge has received honoraria for lectures and attendance at advisory boards from all the manufacturers of statin drugs.

REFERENCES

- 1 Endo A. The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res* 1992;33:1569–82.
- 2 Brown MS, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. *Cell* 1997;89:331–40.
- 3 Vega GL, East C, Grundy SM. Lovastatin therapy in familial dysbeta-lipoproteinaemia: effects on kinetics of apolipoprotein B. *Atherosclerosis* 1998;70:131–43.
- 4 Gaw A, Packard CJ, Murray EF, et al. Effects of simvastatin on apoB metabolism and LDL subfraction distribution. *Arterioscler Thromb* 1993;13:170–89.
- 5 Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–4.
- 6 Betteridge DJ, Khan M. *Statins and coronary artery disease*, 2nd edn. London: Science Press Ltd, 2003.
- 7 Gaw A, Packard CJ, Shepherd J. *Statins: the HMG-CoA reductase inhibitors in perspective*. London: Martin Dunitz, 2000.
- 8 Stein EA, Lane M, Laskarzewski P. Comparison of statins in hypertriglyceridaemia. *Am J Cardiol* 1998;81:66B–69B.
- 9 Jones P, Kafonek S, Laurora I, et al. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolaemia (the CURVES study). *Am J Cardiol* 1998;81:582–7.
- 10 Jones P, Davidson MH, Stein EA, et al. for the STELLAR Study Group. Comparison of efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003;92:152–60.
- 11 Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of cholesterol-lowering treatment; prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet* 2005;366:1267–78.
- 12 Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the adverse event reporting system. *Am J Cardiol* 2006;97:32–43.
- 13 Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol* 2002;40:567–72.
- 14 Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;97:52–60.
- 15 Grundy SM. The issue of statin safety: where do we stand? *Circulation* 2005;111:3016–19.
- 16 Newman CB, Palmer G, Silbershatz H, Szarek M. Comparative safety of atorvastatin 80mg/day versus 10mg/day derived from analysis of 49 completed trials in 12,056 patients. *Am J Cardiol* 2006;97:61–7.
- 17 de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive versus a delayed conservative strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307–16.
- 18 Kjekshus J, Apetrei E, Barrios V, et al. for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;357:2248–61.
- 19 Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1782–90.
- 20 Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent events in acute coronary syndromes: the MIRACL study, a randomized controlled trial. *JAMA* 2001;285:1711–8.