

LOVASTATIN AND BEYOND: THE HISTORY OF THE HMG-COA REDUCTASE INHIBITORS

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In the 1950s and 1960s, it became apparent that elevated concentrations of plasma cholesterol were a major risk factor for the development of coronary heart disease, which led to the search for drugs that could reduce plasma cholesterol. One possibility was to reduce cholesterol biosynthesis, and the rate-limiting enzyme in the cholesterol biosynthetic pathway, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, was a natural target. Here, I describe the discovery and development of lovastatin — the first approved inhibitor of HMG-CoA reductase — and the clinical trials that have provided the evidence for the ability of drugs in this class to reduce the morbidity and mortality associated with cardiovascular disease.

CASE HISTORY

More than 100 years ago the German pathologist Virchow observed that the artery walls of patients dying of occlusive vascular disease, such as MYOCARDIAL INFARCTION, were often thickened and irregular, and contained a yellowish fatty substance subsequently identified as cholesterol. This pathological condition was termed atheroma, the Greek word for porridge. In 1913, Anitschkow and Chalotow showed that feeding cholesterol to rabbits rapidly produces atheromatous disease similar to that found in man. However, physicians were sceptical of any causal link between cholesterol and CORONARY HEART DISEASE (CHD) because most patients with the disease have plasma cholesterol levels not much different from that of the general population average¹. So began the FRAMINGHAM study in the 1950s, led by Dawber, with the initial goal of prospectively examining the relationship between blood cholesterol and other potential risk factors and death from coronary disease. This work established an increasingly firm correlation between high plasma cholesterol and CHD mortality², which was confirmed by many other within-population studies. In addition, the Seven Countries Study led by Keys, which was initiated in the 1950s, showed that northern European countries and the United States had both high plasma cholesterol and

high CHD mortality rates. By contrast, plasma cholesterol and CHD mortality were both substantially lower in southern Europe, and even more so in Japan³. Later investigations established that the association with CHD mortality was attributable mainly to low-density lipoprotein (LDL) cholesterol, which typically comprises about 70% of total cholesterol, whereas high-density lipoprotein (HDL) cholesterol is inversely correlated with CHD mortality. Thus was born the lipid hypothesis, which proposed that elevated total, or more accurately LDL, cholesterol was causally related to coronary disease and that reducing it would reduce the risk of myocardial infarction and other coronary events.

The cholesterol controversy: phase 1

The lipid hypothesis remained controversial for many years, mainly because of the lack of clear evidence that lowering cholesterol provided any clinical benefits. Before the advent of HMG-CoA reductase inhibitors, a number of dietary intervention studies and a few drug studies had reported a reduction in CHD events in patients with and without CHD. Although no individual study was compelling, taken together, a good case could be made that lowering cholesterol reduced the risk of coronary events⁴. On

MYOCARDIAL INFARCTION
Popularly known as a heart attack, this is the death of part of the heart muscle due to sudden loss of blood supply. Typically, the loss of this supply is caused by a complete blockage of a coronary artery containing atherosclerotic plaque by a blood clot.

CORONARY HEART DISEASE (CHD). A condition in which the main arteries supplying the heart contain atherosclerotic plaque, which can cause myocardial infarction (see above) or angina pectoris, in which cardiac blood flow is reduced, leading to heart pain on exercise. Atherosclerotic plaque contains macrophages and cholesterol.

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FRAMINGHAM

Framingham is a Massachusetts town considered representative of the United States population, and the epidemiology of cardiovascular disease still continues to be studied there after more than half a century.

the basis of those studies, and the recently completed National Institutes of Health (NIH) Coronary Primary Prevention Trial, an NIH Consensus Conference convened in 1984 concluded that lowering elevated LDL cholesterol with diet and drugs would reduce the risk of CHD⁵. The NIH accepted the findings of the Consensus Conference and the following year initiated a massive programme to educate physicians and the public about the importance of treating hypercholesterolaemia. However, several important questions remained unanswered, including: would prolonged

treatment be safe? Would women and the elderly benefit? Such questions could not be answered until the advent of the HMG-CoA reductase inhibitors.

Cholesterol manufacture

Most mammalian cells can produce cholesterol. Cholesterol biosynthesis is a complex process involving more than 30 enzymes, and the details of the biosynthetic pathway were worked out in many institutions, including Merck Research Laboratories, mainly in the 1950s and 1960s. The pathway, shown in simplified form in FIG. 1, was a natural target in the search for drugs to reduce plasma cholesterol concentrations, in the hope that these treatments would reduce the risk of CHD. However, early attempts to reduce cholesterol biosynthesis were disastrous. Triparanol, which inhibits a late step in the pathway, was introduced into clinical use in the mid-1960s, but was withdrawn from the market shortly after because of the development of cataracts and various cutaneous adverse effects⁶. These side effects were attributable to tissue accumulation of desmosterol, the substrate for the inhibited enzyme.

The discovery of statins

HMG-CoA reductase is the rate-limiting enzyme in the cholesterol biosynthetic pathway (see FIG. 1). In contrast to desmosterol and other late-stage intermediates, hydroxymethylglutarate is water soluble and there are alternative metabolic pathways for its breakdown when HMG-CoA reductase is inhibited, so that there is no build-up of potentially toxic precursors. HMG-CoA reductase was, therefore, an attractive target. Natural products with a powerful inhibitory effect on HMG-CoA reductase, including ML236B (compactin), were first discovered by the Japanese microbiologist Akira Endo in a fermentation broth of *Penicillium citrinum* in the 1970s, during a search for antimicrobial agents^{7,8} (TIMELINE). Although no HMG-CoA reductase inhibitor has been shown to have useful antimicrobial activity, the possibility that an agent that inhibited the rate-limiting step in the cholesterol biosynthesis pathway could have useful lipid-lowering properties was quickly appreciated by Endo and others.

Compactin was shown to lower plasma cholesterol in the rabbit⁹, monkey¹⁰ and dog¹¹. However, some investigators were led astray by the fact that compactin did not lower plasma cholesterol in the rat¹², which was later shown to result from massive induction of HMG-CoA reductase in rat liver by inhibitors of the enzyme^{13,14}. The dog was found to be a good animal model¹⁵, especially when pretreated with the bile-acid sequestrant cholestyramine. The prototype compound compactin was developed by Sankyo, and was shown to be highly effective in reducing concentrations of total and LDL cholesterol in the plasma of patients with heterozygous familial hypercholesterolaemia^{16,17}. In 1978, Alberts, Chen and others at Merck Research Laboratories found a potent inhibitor of HMG-CoA reductase in a fermentation broth of *Aspergillus terreus*¹⁵. They named their discovery mevinolin; later, the official (USAN) name was established as lovastatin (TIMELINE).

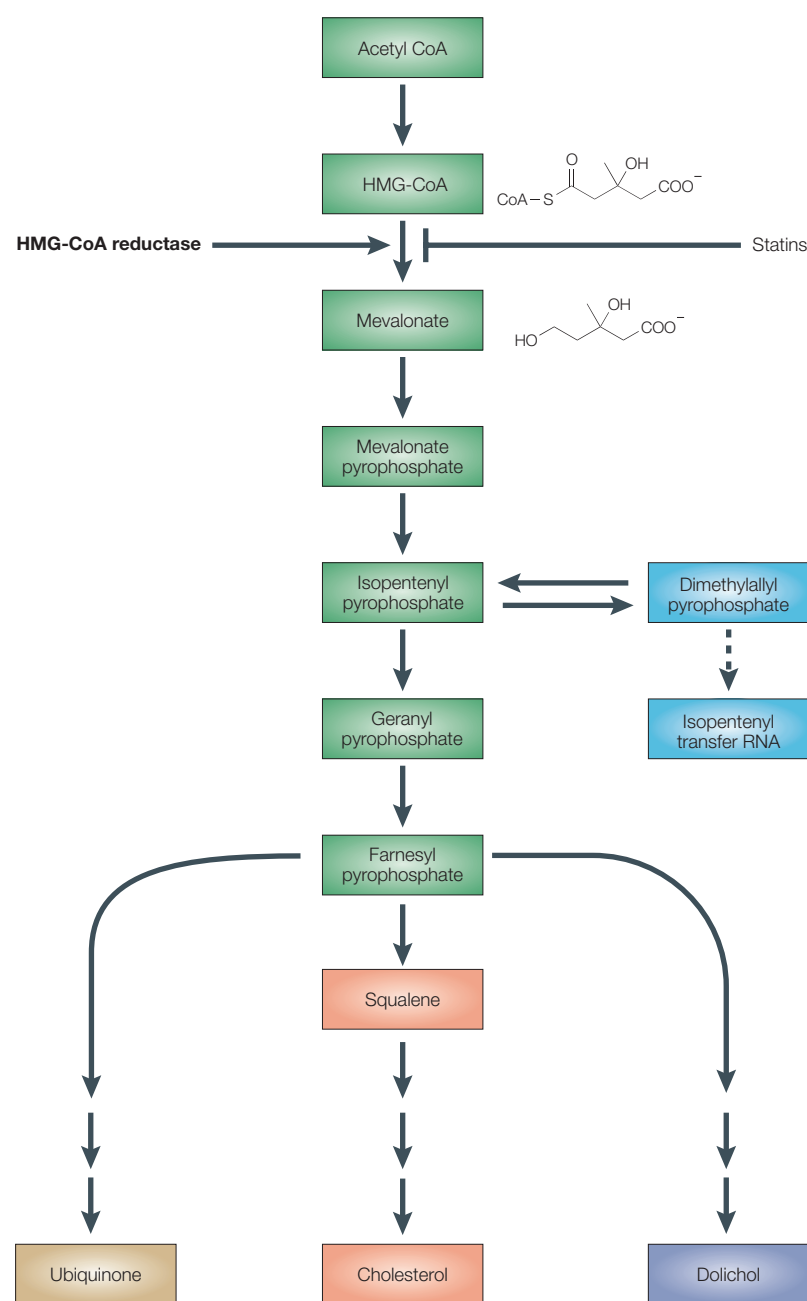
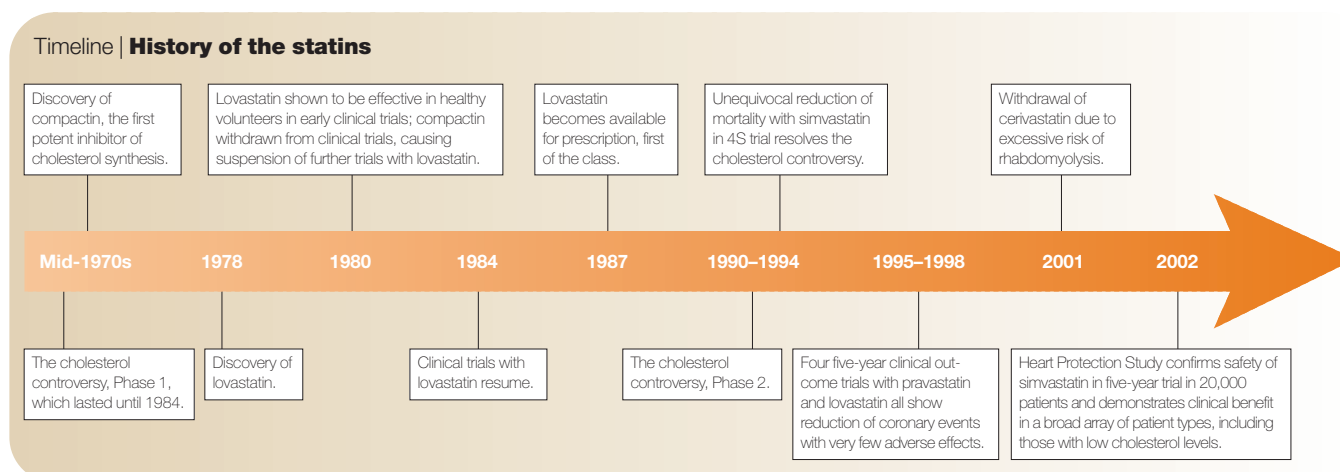


Figure 1 | **The cholesterol biosynthesis pathway.** Cholesterol biosynthesis is a complex process involving more than 30 enzymes. A simplified version is shown here, which highlights the step inhibited by statins, and shows the chemical structures of the starting material (HMG-CoA) and product (mevalonate) of this step.



Lovastatin: a difficult beginning

In April 1980, after animal safety studies had been performed, Merck began clinical trials of lovastatin in healthy volunteers. Lovastatin was shown to be dramatically effective for lowering LDL cholesterol in healthy volunteers, with no obvious adverse effects^{18,19}. However, this promising start was soon to be interrupted. Clinical trials with compactin had been proceeding, but for reasons that have never been made public (but which were believed to include serious animal toxicity) the trials were stopped by Sankyo in September 1980. Because of the close structural similarity between compactin and lovastatin, Merck promptly suspended clinical studies with lovastatin, and initiated additional animal safety studies. The future of the drug seemed extremely doubtful. However, in 1982 some small-scale clinical investigations in very high-risk patients resumed outside Merck. Bilheimer and Grundy in Dallas, Texas, and Illingworth in Portland, Oregon asked Merck for lovastatin to test its effect in selected small groups of patients with severe heterozygous FAMILIAL HYPERCHOLESTEROLAEMIA (FH) (BOX 1) refractory to existing therapy. They observed dramatic reductions in LDL cholesterol^{20,21} with very few adverse effects. Later, Thompson in London found that lovastatin considerably enhanced the hypolipidaemic effect of apheresis in patients with heterozygous FH²².

After the additional animal safety studies with lovastatin revealed no toxicity of the type believed to be associated with compactin, Merck decided, in 1983, to re-initiate the clinical development programme, initially in patients at very high risk of myocardial infarction. Because of concerns about patient safety, this was a difficult decision, reached only after prolonged internal debate. Notwithstanding the excellent tolerability to date in relatively small short-term studies, it was quite possible that more experience in a large number of patients treated chronically, as well as long-term animal toxicology studies, would yield a poor safety profile, including potential carcinogenicity. This would prohibit the development of lovastatin, or at best limit its use to a few ultra-high-risk patients — the ‘ORPHAN DRUG’ scenario.

In randomized, double-blind Phase IIb placebo-controlled studies started in 1984 (TIMELINE), lovastatin was as effective in patients with heterozygous FH²³ and patients with CHD and non-familial hypercholesterolaemia²⁴ as it had been in healthy volunteers¹⁹. These effects were confirmed in larger Phase III studies, in which lovastatin produced much greater reductions in LDL cholesterol than the control agents cholestyramine²⁵ and probucol²⁶, with very few adverse effects. The effects of lovastatin in the Phase IIb studies are shown in FIG. 2.

Lovastatin produced a profound reduction of apolipoprotein-B-containing lipoproteins, especially LDL cholesterol and, to a lesser extent, plasma triglycerides, and a small increase in HDL cholesterol. Observed tolerability continued to be excellent, with very few patients withdrawing from treatment due to adverse effects. In November 1986, Merck applied for regulatory approval of lovastatin. In February 1987, a US FDA advisory panel fully considered the various safety issues arising out of the animal toxicology studies discussed below and the clinical results summarized above. The panel voted unanimously for the approval of the drug, and FDA approval was obtained on 31 August 1987 (TIMELINE). Lovastatin had patent protection only in certain other countries, all of which later granted approval.

Statins enter clinical use

Before 1987, the lipid-lowering armamentarium was limited essentially to dietary changes (reductions in saturated fats and cholesterol), the bile-acid sequestrants (cholestyramine and colestipol), nicotinic acid (niacin), the fibrates and probucol. Unfortunately, all of these treatments have limited efficacy or tolerability, or both. Dietary changes that patients in Western countries will tolerate produce only small changes in total and LDL cholesterol²⁷. The bile-acid sequestrants are moderately effective and not systemically absorbed, but multi-gram doses are required and gastrointestinal tolerability is poor. The fibrates (gemfibrozil, fenofibrate, bezafibrate and others) produce a moderate reduction in LDL cholesterol accompanied by increased HDL

FAMILIAL HYPERCHOLESTEROLAEMIA (FH). This is an autosomal dominant condition characterized by a defective allele coding for the low-density lipoprotein (LDL) receptor, which causes gross elevations of plasma LDL cholesterol.

ORPHAN DRUG
An agent that is useful for diseases too rare to provide more than minimal commercial potential is known as an orphan drug.

Box 1 | **Familial hypercholesterolaemia**

Patients with one defective allele coding for the low-density lipoprotein (LDL) receptor have heterozygous familial hypercholesterolaemia, which is one of the most common monogenic disorders, occurring at an incidence of about 1 in 500. Patients with this condition have LDL cholesterol levels that are typically over twice the population average (which is about 3.5 mmol l⁻¹ in Western countries), and are at high risk of premature coronary heart disease (CHD). The homozygous form of the disease, in which both alleles are defective and which therefore results in essentially non-functioning LDL receptors, occurs in about one in a million live births. LDL cholesterol is typically more than 15 mmol l⁻¹ and CHD usually develops in childhood, providing additional evidence for the lipid hypothesis.

cholesterol and a substantial reduction in triglycerides. Because they are well tolerated, these drugs have been more widely used. Probucol produces only a small reduction in LDL cholesterol but also reduces HDL cholesterol, which, because of the strong inverse relationship between HDL cholesterol level and CHD risk, is generally considered undesirable. This drug is no longer marketed in most countries.

When lovastatin became available for prescription use, physicians were able, for the first time, to easily obtain large reductions in plasma cholesterol. Lovastatin at its maximal recommended dose of 80 mg daily produced a mean reduction in LDL cholesterol of 40%^{23–26}, a far greater reduction than could be obtained with any of the treatments available at the time. Equally important, the drug produced very few adverse effects, and with once- or twice-daily dosing, was easy for patients to take. For these reasons, lovastatin was rapidly accepted by prescribers and patients. After the early safety concerns were resolved by numerous animal safety studies and an intensive clinical research programme that continued well past its regulatory approval, including a Phase IV study in over 8,000 patients²⁸, the efficacy and tolerability of the drug paved the way for its success. Such are the uncertainties of drug development: it is a pleasant irony that lovastatin, once a potential orphan

drug, went on to revolutionize the treatment of hypercholesterolaemia (and achieve peak annual sales of more than US \$1 billion). Unfortunately, the reverse is more often true: a promising drug produces unexpected clinical toxicity that leads to limited use or even withdrawal from the market.

The second entrant, simvastatin, which differs from lovastatin only in that it has an additional side chain methyl group, was initially approved for marketing in Sweden in 1988 and subsequently worldwide. Pravastatin (discovered by Sankyo after the failure of compactin) followed in 1991, fluvastatin in 1994, atorvastatin in 1997, cerivastatin in 1998 (of which more below), and rosuvastatin in 2003. As noted above, lovastatin is a fermentation product. Simvastatin is a semisynthetic derivative of lovastatin, and pravastatin is derived from the natural product compactin by biotransformation, whereas all other HMG-CoA reductase inhibitors are totally synthetic products. The structures of these drugs are shown in FIG. 3. The generic names for all HMG-CoA reductase inhibitors end with 'statin', and the members of this class are today often referred to as 'statins', as opposed to the formal, although rather cumbersome, class name 'HMG-CoA reductase inhibitors'. The term statin will be used henceforward in this article. All inhibitors of HMG-CoA reductase produce a qualitatively similar effect on the lipid profile. The mean reduction in LDL cholesterol attainable with the maximal recommended dose of different statins ranges from 35 to 55%.

Adverse effects of statins

Statins produce significant toxicity at high doses in a variety of animal species. These effects include increases in hepatic transaminases, atypical focal hyperplasia of the liver, squamous epithelial hyperplasia of the rat fore stomach (an organ not present in man), cataracts, vascular lesions in the central nervous system (CNS), skeletal muscle toxicity, testicular degeneration and, although the statins are clearly not genotoxic, tumours of the liver and other sites (details can be found in the product circulars of the individual statins). It has been shown, where it has been practical to conduct the experiment, that these effects can be prevented by administering mevalonate^{29,30}, the product of the reaction catalysed by HMG-CoA reductase. This indicates that these toxic effects are mostly, if not entirely, attributable to extreme inhibition of the enzyme at high doses²⁹. So Merck, and the regulatory agencies considering the marketing application submitted by Merck, were faced with a wide range of animal toxicological effects, as well as the history of compactin and the known central role of the cholesterol biosynthesis pathway in many physiological processes, including the production of steroids and cell membranes. More than a decade would pass between the introduction of lovastatin and the demonstration that it could reduce the risk of coronary events³¹. It might have never been possible to develop a statin were it not for the mid-century epidemic of CHD, the powerful epidemiological evidence linking it to elevated plasma cholesterol and the

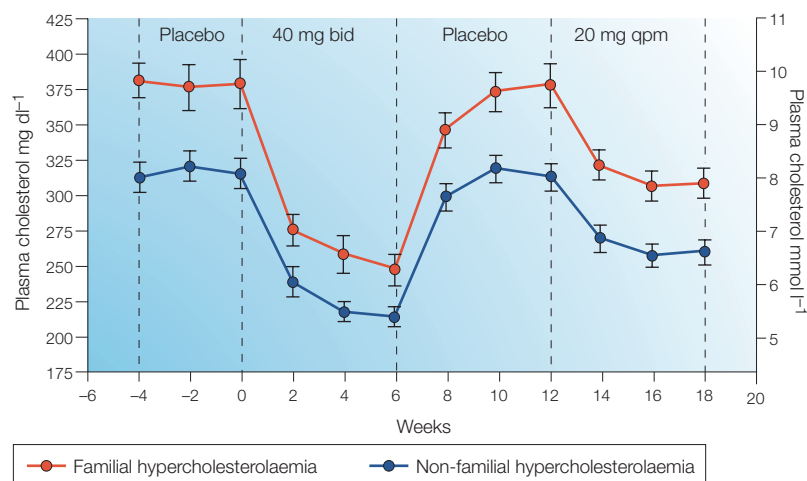


Figure 2 | **Plasma cholesterol changes in the Phase IIb studies of lovastatin.** Effect of lovastatin by time and dose on plasma cholesterol in Phase IIb studies in patients with familial hypercholesterolaemia (FH), and high-risk hypercholesterolaemic patients without FH. Bid, twice daily; qpm, once daily in the evening.

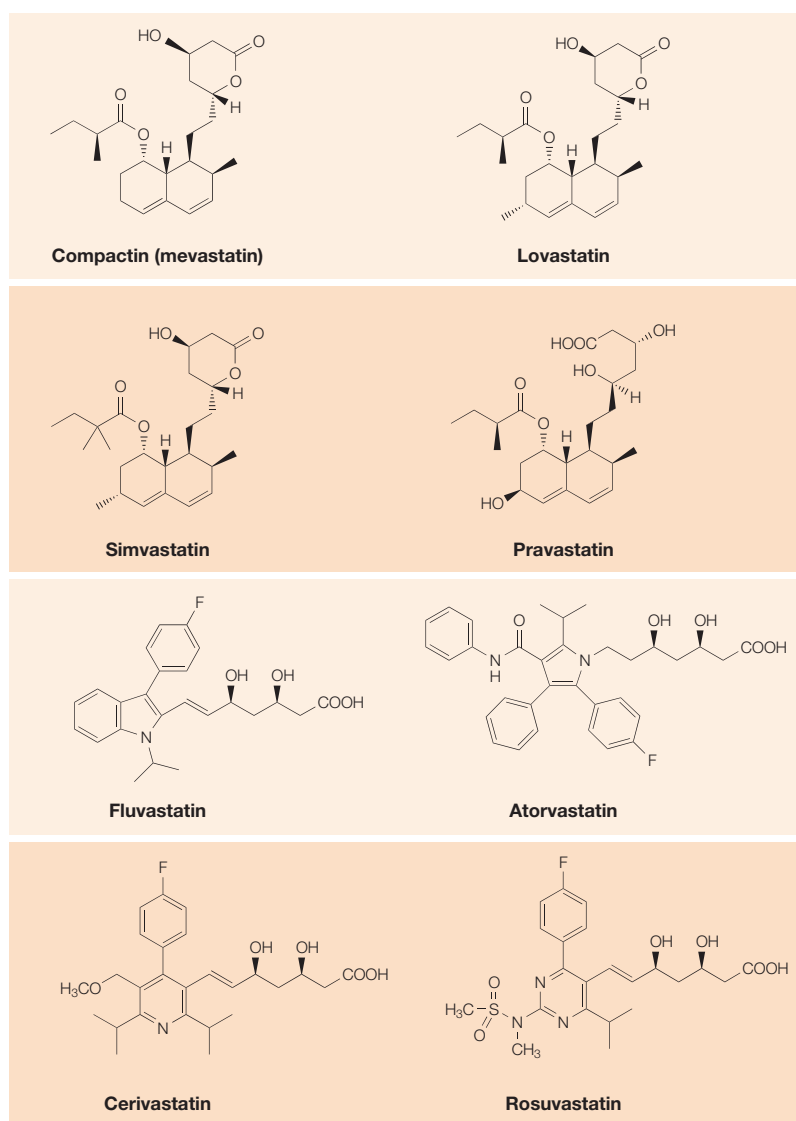


Figure 3 | Structures of the statins. Compactin and lovastatin are natural products. Pravastatin is derived from compactin by biotransformation, and simvastatin is a semisynthetic derivative of lovastatin. All other statins shown are totally synthetic.

lack of any well-tolerated therapy capable of reducing it much, together with the limited data from randomized controlled clinical trials^{32,33} that indicated that reduction of LDL cholesterol could reduce the risk of myocardial infarction. Fortunately, except for rare cases of myopathy and marked but asymptomatic increases in hepatic transaminases, none of the adverse effects found in animals occur at human therapeutic doses.

It has required considerable effort in large long-term clinical trials and shorter specialized studies to establish the safety of statins. Five-year trials have been published with simvastatin^{34–36}, pravastatin^{37–39} and lovastatin³¹. A smaller four-year trial with fluvastatin has also been reported⁴⁰, as has a recent large trial with atorvastatin with 3.3 years follow-up⁴¹. The observation of cataracts in animal toxicology studies was of particular concern because of the experience with triparanol⁶, as noted

above. When lovastatin and simvastatin were first marketed, slit-lamp examination was required to detect possible lens opacities at an early stage. Several studies using either specialized techniques in relatively small patient populations^{42–45}, or routine slit-lamp examination in large populations^{35,46}, showed that lens opacities occurred with similar frequencies in the active and placebo groups. Therefore, cataracts are no longer considered a risk of statin therapies. Although monitoring for liver function test abnormalities is still recommended, there is little evidence that statins produce clinical hepatitis, as opposed to biochemical abnormalities⁴⁷. If they do so, the risk is very small. In large five-year placebo-controlled trials, more than 4,000 cases of cancer have been recorded, split virtually equally between the active and placebo groups^{36,48}. There has been no good evidence of any increase in the risk of cancer at any particular site^{36,48}. In the Scandinavian Simvastatin Survival Study (4S), there was a trend towards fewer cancers among the patients originally randomized to simvastatin⁴⁹ after seven years (an additional two years after the end of the study). Thus, an increased risk of cancer has also largely disappeared as a concern. Finally, suggestions that the more lipid-soluble statins lovastatin and simvastatin might produce adverse effects on the CNS, such as sleep disturbances, were also dispelled by careful clinical studies^{50–55} and long-term trials^{31,35}.

In yet another irony of the history of statins, the only important adverse effect of the class — myopathy (BOX 2) or, in its more severe form, rhabdomyolysis — was not among the plethora of abnormalities detected in the original animal safety assessment studies with lovastatin, although it was discovered later in animal studies with lovastatin and other statins. It was first reported in a cardiac transplant patient receiving the immunosuppressive cyclosporine, in addition to gemfibrozil⁵⁶. Both of these drugs were later found to substantially increase the risk of myopathy with statins^{57,58}. This patient was participating in a compassionate use programme in which Merck made lovastatin available to very high-risk patients before its approval for marketing. Such programmes, which typically include patients excluded from controlled clinical trials, can reveal adverse effects not otherwise easily detected. At about the same time, myopathy was also detected in a single patient taking lovastatin in a Phase III clinical trial²⁵.

The risk of myopathy with statins is increased by concomitant administration of certain other drugs, particularly gemfibrozil (see below), and, to a lesser extent, possibly some other fibrates, and niacin. In addition, for statins that are substrates for **cytochrome P450 3A4** (that is, lovastatin, simvastatin and atorvastatin), the risk of myopathy is increased by the concomitant administration of potent inhibitors of this enzyme, which include cyclosporine, the antidepressant nefazodone, and certain antifungal azoles, macrolide antibiotics and protease inhibitors used to treat HIV infection⁵⁸. Recently, amiodarone has been found to substantially increase the risk of myopathy with simvastatin given at high dosage. Full details are available in the

Box 2 | Statin-induced myopathy

Few drugs have toxic effects on skeletal muscle, but all statins occasionally cause myopathy. This adverse effect was recently thoroughly reviewed by Ballantyne *et al.*⁵⁹. The incidence increases with dose, but is typically less than 0.1%. In the context of statin therapy, myopathy is generally defined as unexplained muscle pain or weakness accompanied by a grossly elevated creatine kinase concentration, >10 times the upper limit of normal. Rhabdomyolysis is a severe form of myopathy that can require the patient to be hospitalized, and can result in myoglobinuria that can lead to acute renal failure. Fortunately, the adverse effect is confined to skeletal muscle, and cardiomyopathy has never been associated with any statin. Prompt recovery occurs on cessation of therapy, although there have been very rare cases in which treatment continued despite muscle symptoms, and death occurred due to acute renal failure. Myopathy can be prevented in a rat model by administering mevalonate³⁰, the product of the inhibited enzyme. Beyond this, however, the mechanism of statin-induced myopathy is still not understood 15 years after it was first reported.

product circulars of individual statins. It is important for patients to be aware of the risk of myopathy and to promptly report unexplained muscle symptoms, and for prescribers to take into account these drug interactions, particularly when using statins at high dosages. Nevertheless, with all marketed statins, myopathy/rhabdomyolysis is a rare adverse effect (BOX 2)⁵⁹. Therefore, although they account for a substantial minority of all cases, in absolute terms myopathy/rhabdomyolysis due to drug interactions are also rare.

Statin mechanisms

The mechanism of the reduction in plasma cholesterol by statins is not simply reduction in cholesterol biosynthesis. In the 1970s, Brown and Goldstein worked out the central role of the hepatic LDL receptor in determining the concentration of LDL cholesterol in plasma and its role in FH (BOX 1)⁶⁰, for which they received the Nobel Prize in 1985.

Inhibition of HMG-CoA reductase reduces levels of mevalonate^{61,62}, which leads to a reduction in the regulatory sterol pool, which in turn causes upregulation of HMG-CoA reductase⁶³, other enzymes of cholesterol biosynthesis^{64,65}, and most importantly the LDL receptor^{66,67}. Although the LDL receptor was not the original target that the discoverers of compactin^{7,8} and lovastatin¹⁵ were aiming at, the work of Brown and Goldstein and others showed that induction of this receptor is crucial to the effectiveness of the statin drug class.

Most of the data on LDL receptor induction have emerged from work in animals, although some have been generated from human studies. Reihner *et al.* treated ten patients undergoing elective cholecystectomy with pravastatin 20 mg twice daily for three weeks before surgery⁶⁸. A liver specimen was obtained from each patient at operation. Microsomal HMG-CoA reductase activity, analysed *in vitro* in the absence of the inhibitor, was increased about 12-fold and the expression of LDL receptors approximately doubled. So, statins lower human plasma cholesterol by increasing the uptake of LDL via the LDL receptor. Although LDL receptor upregulation is clearly the primary mechanism of action, these drugs also decrease the production of apolipoprotein-B-containing lipoproteins by the liver⁶⁹.

Consistent with this mechanism is the fact that high doses of atorvastatin⁷⁰ and simvastatin⁷¹ produce moderate reductions of LDL cholesterol in patients with homozygous FH, who lack the LDL receptor.

The cholesterol controversy: phase 2

In 1989, Daniel Steinberg, one of the founding fathers of modern lipidology, published a paper titled 'The cholesterol controversy is over. Why did it take so long?'⁷². However, this declaration was soon to be challenged. Although the basic lipid hypothesis had been validated (see above), the movement towards treating hypercholesterolaemia (dismissed in some quarters as 'lipid evangelism') came under fire from a number of sources. The clinical trial evidence was largely limited to middle-aged men, and the generalizability to women and the elderly was questioned. Overviews of trials of treatments from the pre-statin era published in 1990 (REF. 73) and 1992 (REF. 74) indicated that although CHD events might be reduced, survival was not improved, particularly in the absence of established CHD, because the observed small reduction of CHD deaths seemed to be offset by an apparent increase in non-cardiac mortality, including cancer and violent deaths. This led Davey Smith and Pekkanen to title their 1992 overview 'Should there be a moratorium on cholesterol-lowering drugs?'⁷⁴. Nevertheless, expert panels in Europe and in the United States continued to recommend, where appropriate, the addition of drugs to dietary changes to reduce elevated cholesterol levels^{75,76}, especially in patients with CHD. However, because of the ongoing vigorous debate, the use of cholesterol-lowering drugs was often rejected, especially in Britain and Scandinavia.

While this controversy raged, the adoption of statin therapy slowed. Using quantitative angiography⁷⁷⁻⁸¹ or ultrasound^{82,83}, statins were shown to slow the progression of atherosclerotic lesions. However, these effects on vessel anatomy were quite small, and with each trial including only a few hundred patients typically followed for two years, little new safety information was obtained. However, the publication in November 1994 of the results of the Scandinavian Simvastatin Survival Study (4S)³⁴ marks a turning point in medical thinking (TIMELINE). A total of 4,444 patients with CHD and total plasma cholesterol 5.5–8.0 mmol l⁻¹ on a lipid-lowering diet were randomly allocated on a double-blind basis to simvastatin 20–40 mg once daily or placebo for five years. As shown in TABLE 1, there was an unequivocal 30% reduction in all-cause mortality ($p = 0.0003$), due to a 42% reduction in coronary deaths. These effects on mortality were accompanied by a 34% reduction in major coronary events (non-fatal myocardial infarction plus CHD death) and a 37% reduction in revascularization procedures. Importantly, there was no indication of any offsetting increase in non-cardiovascular mortality, and in particular, no increase in violent deaths or the incidence of cancer^{34,35}. Only one patient in the simvastatin group developed myopathy. These results reassured those who argued that lowering cholesterol might reduce CHD events but not total mortality, including the distinguished cardiologist Michael Oliver,

a prominent and long-time sceptic whose papers often had titles that left little doubt about their author's views^{84,85}. Shortly after the publication of the results of 4S, Oliver *et al.* published an editorial with the equally unambiguous title 'Lower patients' cholesterol now'⁸⁶.

The magnitude of the reduction in LDL cholesterol obtainable with statins is much greater than with the earlier treatments used in previous clinical trials. Clinical trial methodology had advanced; most importantly, there was increasing recognition that clinical outcome trials have to include a large number of patients and a long duration of treatment to provide sufficient statistical power for unequivocal results⁸⁷. For these reasons, the 4S trial was the first of a series of clinical trials with simvastatin^{34,36}, pravastatin^{37–39}, lovastatin³¹, fluvastatin⁴⁰ and atorvastatin⁴¹ that established that these statins not only substantially reduced the risk of cardiovascular events, but did so without any increase in non-cardiovascular mortality or cancer. The risk of CHD events was reduced both in patients who already had CHD (secondary prevention)^{34,36,40,41}, and in those who did not (primary prevention)^{31,36,37}. The Heart Protection Study (HPS)³⁶ is by far the largest of the placebo-controlled five-year statin trials, and, in terms of total number of patient years included in the follow-up, one of the largest randomized clinical trials ever completed. In the previous statin trials, because age at entry was limited to 70 years in most of these studies, and because women comprised less than one-fifth of the total patient population of these trials, the evidence for benefit in women and elderly patients was not completely definitive. These trials also included very few patients with diabetes who did not have CHD. In HPS, more than 20,000 patients in the United Kingdom with CHD, or at high risk of CHD due to cerebrovascular or peripheral vessel disease, or diabetes, were randomized to simvastatin 40 mg or placebo for five years. The only lipid-exclusion criterion was total plasma cholesterol < 3.5 mmol l⁻¹ (135 mg dl⁻¹), which excluded less than 2% of potential participants.

HPS confirmed and expanded previous evidence, including firmly establishing the benefit of simvastatin in women, and its effectiveness for reduction of the risk not only of CHD events such as myocardial infarction, but also of strokes (TIMELINE). It also provided new and compelling evidence for the beneficial effects of simvastatin on clinical outcomes in various large patient groups that had scarcely been studied. Most importantly, significant reductions in the risk of major vascular events were observed in patients with diabetes but

no CHD, patients with cerebrovascular or peripheral vessel disease but no CHD, patients aged 70 or older, and patients with LDL cholesterol well below average (<100 mg dl⁻¹ (2.6 mmol l⁻¹)) at entry. These effects had not been previously reported for any statin. The tolerability and safety of simvastatin was confirmed yet again; the incidence of myopathy, including rhabdomyolysis, was <0.1%. The effectiveness of simvastatin against major vascular events by baseline LDL cholesterol is shown in TABLE 2.

Do statins have any therapeutic effects that are not dependent on changes in lipids and lipoproteins? This question has been asked for many years, with little evidence to support an affirmative answer as yet; the effects on cardiovascular disease outcomes can be adequately explained by the lipid effects⁸⁸. Several investigators have suggested that statins could ameliorate the endothelial dysfunction that is associated with atherosclerotic disease. However, the largest placebo-controlled study to test this hypothesis (which involved simvastatin) was negative⁸⁹. Others have suggested that statins could have effects outside of the cardiovascular system. For example, animal and epidemiological studies have led to speculation that statins could reduce cognitive impairment and the risk of bone fracture in the elderly. Again, both of these hypotheses were tested in HPS, with completely negative results³⁶. Investigations of other possible beneficial effects continue, such as in inflammatory and immunological diseases, and any clearly positive results would be of great interest. For example, preliminary results from a small pilot study⁹⁰ indicate that simvastatin might have beneficial effects in multiple sclerosis. If proven in larger randomized controlled studies, this would be a very important finding.

The withdrawal of cerivastatin

The first year of the new millennium was to mark a setback in the history of the statins. As 2001 began, the perceived safety of the class was well established by more than a decade of prescription use in many millions of patients, as well as hundreds of clinical trials, including the large outcome studies with simvastatin, pravastatin and lovastatin that preceded HPS and included a total of about 30,000 patients studied for five years⁴⁸. However, in August 2001, the newest statin, cerivastatin, which had been introduced in 1998, was withdrawn from the market by its manufacturer because of a large number of reports of rhabdomyolysis, of which more than 50 cases were fatal^{59,91,92}. The risk of rhabdomyolysis was much higher with cerivastatin than with the other statins^{59,91,92}, and extensive litigation relating to cerivastatin is ongoing⁹².

A substantial minority of the reported cases of rhabdomyolysis occurred during concomitant use of gemfibrozil and cerivastatin⁹¹. Gemfibrozil increases the risk of myopathy with all statins; the mechanism is probably partly pharmacodynamic, as gemfibrozil can cause myopathy alone⁹³, and partly pharmacokinetic. In the case of cerivastatin, the pharmacokinetic interaction is particularly marked; gemfibrozil was recently reported to increase the plasma concentration

Table 1 | Mortality by cause in 4S

Cause of death	Simvastatin (n = 2,221)	Placebo (n = 2,223)	Risk reduction
Coronary	111	189	42% (p<0.00001)
Other cardiovascular	18	25	
Non-cardiovascular	46	49	
All causes	182	256	30% (p = 0.0003)

4S, Scandinavian Simvastatin Survival Study.

Table 2 | **Simvastatin reduces major vascular events regardless of baseline LDL cholesterol***

Lipid levels at entry (LDL cholesterol)	Number of patients with major vascular events [‡]		Rate ratio and 95% confidence interval [§]	
	Simvastatin (10,269 patients)	Placebo (10,267 patients)	Statin better	Placebo better
<100 mg dl ⁻¹	282 (16.4%)	358 (21.0%)		
≥100<130 mg dl ⁻¹	668 (18.9%)	871 (24.7%)		
≥130 mg dl ⁻¹	1,083 (21.6%)	1,356 (26.9%)		
All patients	2,033 (19.8%)	2,585 (25.2%)		

*Even below 100 mg dl⁻¹ (2.6 mmol l⁻¹; 1 mmol l⁻¹ = 38.7 mg dl⁻¹). [‡]A composite endpoint comprising coronary heart disease death, non-fatal myocardial infarction, stroke, and coronary or peripheral revascularization. [§]The size of the squares is proportional to the number of patients with events and the width of the diamond is the 95% confidence interval. LDL, low-density lipoprotein. Source: <http://www.hpsinfo.org> (adapted from slide 41).

of cerivastatin approximately fivefold⁹⁴. On a milligram basis, cerivastatin was far more potent than any other statin, with a maximal recommended dose that was originally 0.3 mg, and later extended to 0.4 mg and then 0.8 mg; the usual doses of all the other statins range between 10 and 40 mg, with a maximum of 80 mg. For drugs in general, there is little relationship between milligram potency and achievable efficacy, and at 0.4 mg cerivastatin produced a mean reduction in LDL cholesterol of approximately 36%⁹⁵, much less than that achievable with maximal doses of simvastatin or atorvastatin. The extension of the dosage range to 0.8 mg provided additional LDL cholesterol reduction, but it substantially increased the risk of rhabdomyolysis, and made clear that the benefit/risk relationship was much less favourable than for the other statins.

It is not known why cerivastatin is more myotoxic than other statins. Although regulatory agencies were careful to point out that their concern was specific to cerivastatin, its withdrawal shook the confidence of some physicians in the safety of statins in general⁵⁹. Prescription growth rates for the class, which had approached 20% annually in many countries, fell to single digits in 2002. This is unfortunate, as despite the abundance of evidence for benefit in the large statin outcome trials^{34,36-41}, many high-risk patients still go untreated, with the result that preventable major events such as myocardial infarction and stroke are not prevented. The number of major cardiovascular events prevented in these outcome trials is orders of magnitude greater than the number of cases of rhabdomyolysis produced⁵⁹.

Future directions

Although CHD is still the leading cause of death in most industrialized countries (except those of East Asia), in many Western countries age-adjusted CHD mortality has declined by about half from its peak in the 1960s. There are many reasons for this, not all well understood, but certainly the availability and use of drugs including not only statins, but also β-adrenoceptor antagonists, aspirin, and angiotensin-converting enzyme inhibitors, all proven by multiple large placebo-controlled trials to reduce risk, is a major

contributor⁹⁶. Although much remains to be done, including addressing the high rates of CHD mortality and morbidity in Eastern Europe and the rising rates in much of the developing world, this must surely be one of the major medical accomplishments of the last quarter of the twentieth century⁹⁶.

In HPS³⁶, the proportional risk reduction was similar in patients with low and high levels of LDL cholesterol. There was no evidence for any threshold below which lowering LDL cholesterol would be futile, and no evidence that adverse effects result from reducing LDL cholesterol to very low levels. This supports the idea that every patient with atherosclerotic disease has LDL cholesterol that is too high for him or her, no matter how low it might be relative to the population. The paradigm of treating in order to achieve a target level of LDL cholesterol, enshrined in various guidelines for many years, might be obsolete^{36,96}. Rather, in high-risk patients, the objective probably should be to lower LDL cholesterol as far as possible consistent with safety, regardless of the pretreatment level. Ongoing trials with simvastatin (Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH))⁹⁷ and atorvastatin (Treating to New Targets (TNT))⁹⁸, which are comparing high versus low doses of the drugs, should shed further light on this issue within the next two years.

Physicians might attempt to obtain even greater reductions in LDL cholesterol than provided by a statin alone, by adding other agents. However, this has been difficult to achieve. Fibrates and niacin increase HDL cholesterol and reduce triglycerides, but generally provide little additional reduction in LDL cholesterol when added to a statin. Bile-acid sequestrants, which are anion exchange resins, have long been available to provide additional lowering of LDL cholesterol when a statin alone is insufficient, but these agents are inconvenient to take because of the large doses required; in addition, they cause adverse gastrointestinal effects in many patients. However, ezetimibe, a new well-tolerated drug that lowers LDL cholesterol with a once-daily 10 mg dose by inhibiting cholesterol absorption from the gut, is becoming available in many countries. Ezetimibe can be used together with any

statin to substantially augment reductions in LDL cholesterol⁹⁹. This allows very low LDL cholesterol levels to be achieved with very few adverse effects.

In no other drug class has the importance of large long-term, placebo-controlled, clinical-outcome trials to properly evaluate benefit and risk been more clearly and abundantly demonstrated than with statins. Fortunately, as previously discussed, the benefit/risk relationship has proved very favourable. Further large, placebo-controlled trials in patient populations hitherto under-studied are ongoing or commencing. These include, for example, studies in patients with a history of stroke (Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) with atorvastatin), chronic renal failure (Die Deutsche Diabetes Dialyse Studie (4D) with atorvastatin, Study of Heart And Renal Protection (SHARP) with simvastatin and ezetimibe combined, and A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events (AURORA) with rosuvastatin), and aortic stenosis (Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) with simvastatin and ezetimibe combined).

In many countries one or both of the first two statins — lovastatin and simvastatin — are now available as generic products, which should increase access to statin therapy in health care systems with limited resources. Some statins might be available without a prescription ('over-the-counter' or OTC) at low doses in the United States, the United Kingdom and possibly other countries within the near future. OTC use is proposed for primary prevention in people without atherosclerotic vascular disease or diabetes who are at moderate risk of CHD events due to hypercholesterolaemia.

This would involve another paradigm shift: traditionally, prescription drugs that become available OTC are for acute conditions such as pain or inflammation, not preventive medicine for asymptomatic chronic disorders like hypercholesterolaemia. Whether or not medical and regulatory thinking will accommodate OTC statins remains to be seen. If so, the wheel will surely have turned full circle: from a potential orphan drug, to widely prescribed agents that reduce cardiovascular morbidity and mortality, to products available without a prescription.

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