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ORIGINAL ARTICLE

Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update

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ABSTRACT

Statins are the treatment of choice for the management of hypercholesterolaemia because of their proven efficacy and safety profile. They also have an increasing role in managing cardiovascular risk in patients with relatively normal levels of plasma cholesterol. Although all statins share a common mechanism of action, they differ in terms of their chemical structures, pharmacokinetic profiles, and lipid-modifying efficacy. The chemical structures of statins govern their water solubility, which in turn influences their absorption, distribution, metabolism and excretion. Lovastatin, pravastatin and simvastatin are derived from fungal metabolites and have elimination half-lives of 1–3 h. Atorvastatin, cerivastatin (withdrawn from clinical use in 2001), fluvastatin, pitavastatin and rosuvastatin are fully synthetic compounds, with elimination half-lives ranging from 1 h for fluvastatin to 19 h for rosuvastatin. Atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin are relatively lipophilic compounds. Lipophilic statins are more susceptible to metabolism by the cytochrome P_{450} system, except for pitavastatin, which undergoes limited metabolism via this pathway. Pravastatin and rosuvastatin are relatively hydrophilic and not significantly metabolized by cytochrome P_{450} enzymes. All statins are selective for effect in the liver, largely because of efficient first-pass uptake; passive diffusion through hepatocyte cell membranes is primarily responsible for hepatic uptake of lipophilic statins, while hydrophilic agents are taken up by active carrier-mediated processes. Pravastatin and rosuvastatin show greater hepatoselectivity than lipophilic agents, as well as a reduced potential for uptake by peripheral cells. The bioavailability of the statins differs greatly, from 5% for lovastatin and simvastatin to 60% or greater for cerivastatin and pitavastatin. Clinical studies have demonstrated rosuvastatin to be the most effective for reducing low-density lipoprotein cholesterol, followed by atorvastatin, simvastatin and pravastatin. As a class, statins are generally well tolerated and serious adverse events, including muscle toxicity leading to rhabdomyolysis, are rare. Consideration of the differences between the statins helps to provide a rational basis for their use in clinical practice.

INTRODUCTION

Lipid-modifying interventions have been shown to decrease the risk of coronary heart disease (CHD) both in patients with hypercholesterolaemia and in those with relatively normal levels of low-density lipoprotein cholesterol (LDL-C). This has prompted expert panels in Europe, the USA and elsewhere to recommend dietary changes and, if necessary, lipid-modifying therapy to decrease elevated cholesterol concentrations,

particularly LDL-C [1,2]. Several classes of lipid-modifying drugs are available, including bile acid-binding resins (e.g. cholestyramine, colestipol, colesevalam), nicotinic acid (niacin), the fibrates (e.g. fenofibrate, clofibrate, gemfibrozil, bezafibrate), and more recently the cholesterol-absorption inhibitors (e.g. ezetimibe). On the basis of clinical trial evidence, the most commonly prescribed lipid-modifying therapies are the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as the statins. HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol synthesis. Competitive inhibition of this enzyme by the statins decreases hepatocyte cholesterol synthesis (*Figure 1*). The associated reduction in intracellular cholesterol concentration induces LDL-receptor expression on the hepatocyte cell surface, which results in increased extraction of LDL-C from the blood and decreased circulating LDL-C concentrations [3]. Statins also have beneficial effects on other lipid parameters, including increases in high-density lipoprotein cholesterol (HDL-C) concentration and decreases in triglyceride concentration [4]. Secondary mechanisms by which statins may reduce levels of atherogenic lipoproteins include inhibition of hepatic synthesis of apolipoprotein B100 and a reduction in the synthesis and secretion of triglyceride-rich lipoproteins [5,6]. In addition, statins may exert beneficial cardiovascular effects independent of their lipid-modifying properties [7]. These pleiotropic properties may be explained by inhibition of synthesis of nonsteroidal isoprenoid compounds, which are also produced from mevalonic acid (*Figure 1*) [8], and include improvement of endothelial cell function, modification of inflammatory responses, and reduction of smooth muscle cell proliferation and cholesterol accumulation [7,9].

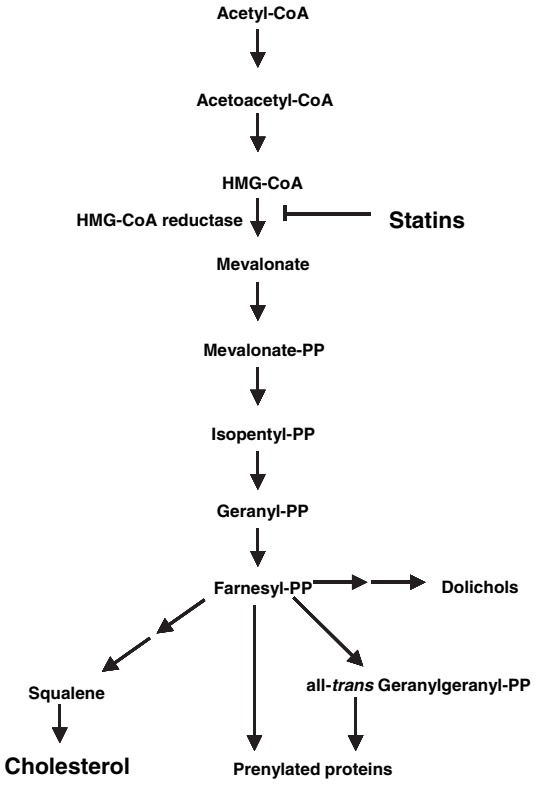

Figure 1 The mammalian mevalonate pathway; PP, pyrophosphate. Adapted from Corsini et al. [9].

Large-scale clinical trials have demonstrated that the statins substantially reduce cardiovascular-related morbidity and mortality in patients with and without existing CHD [10–17]. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis, resulting in fewer new lesions and total occlusions compared with untreated hypercholesterolaemic patients [8,18,19]. This has been suggested to be a consequence of the shrinkage of the lipid core of the atherosclerotic plaque, avoiding plaque rupture that would otherwise trigger intramural haemorrhage and intraluminal thrombosis [8].

Seven statins are now approved for clinical use in at least one country (*Table I*). In general, statins are regarded as a remarkably safe and well-tolerated class of drugs, despite the withdrawal of cerivastatin in 2001 [20]. This paper aims to provide an update of the chemical and pharmacokinetic properties of statins, as well as reviewing their lipid-modifying and safety profiles.

Chemistry and functional properties

Lovastatin, pravastatin and simvastatin are fungal-derived inhibitors of HMG-CoA reductase, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin and rosuvastatin are fully synthetic compounds [21]. The chemical structures of the different statins are shown in *Figure 2*. These structures can be broadly divided into three parts [22]: an analogue of the target enzyme substrate, HMG-CoA; a complex hydrophobic ring structure that is covalently linked to the substrate analogue and is involved in binding of the statin to the reductase enzyme; side groups on the rings that define the solubility properties of the drugs and therefore many of their pharmacokinetic properties. Atorvastatin, fluvastatin, lovastatin and simvastatin are relatively lipophilic compounds, while pravastatin

Table I Comparative efficacy of the different statins on various lipid fractions.

	Atorvastatin	Cerivastatin[a]	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin
Serum LDL-C reduction (%)[b]	50	28	24	34	34	41	63	48
Serum HDL-C increase (%)[b]	6	10	8	9	12	12	10	–[c]
Serum triglyceride reduction (%)[b]	29	13	10	16	24	18	28	23

[a]Voluntarily withdrawn from clinical use; [b]this effect was elicited in patients with hypercholesterolaemia by a daily dose of 40 mg for atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin and rosuvastatin, 4 mg for pitavastatin and 0.3 mg for cerivastatin [60,73,74]; [c]no significant effect reported.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

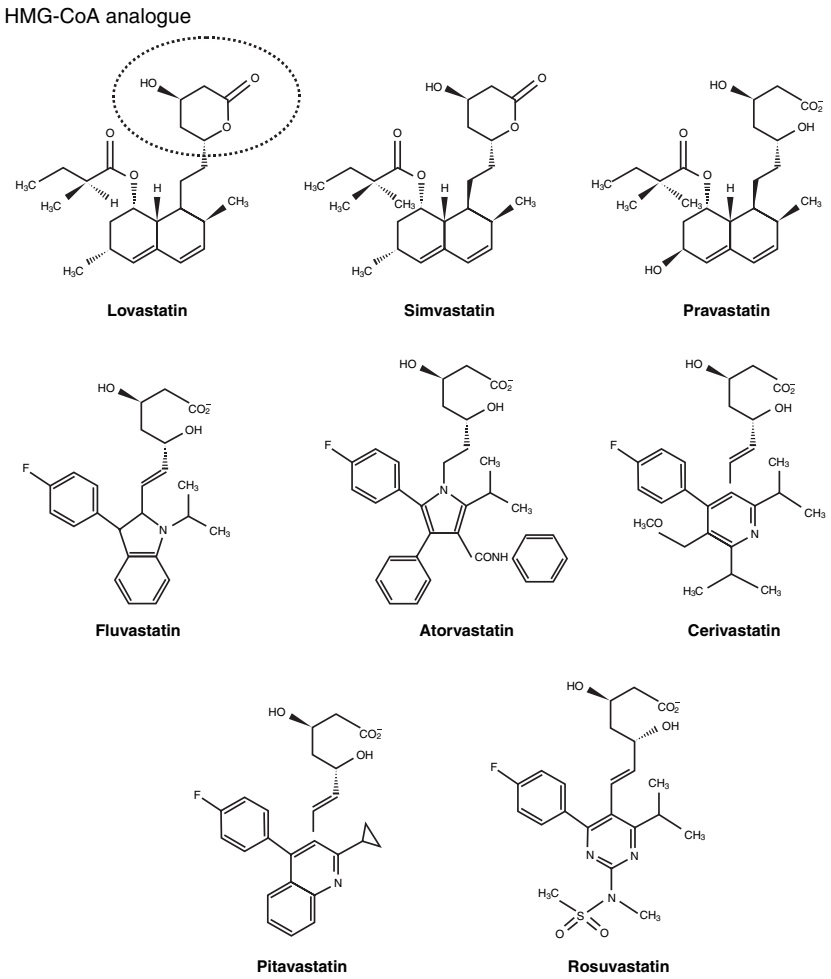

Figure 2 Chemical structures of the statins.

and rosuvastatin are more hydrophilic as a result of a polar hydroxyl group and methane sulphonamide group, respectively [23,24].

All statins are competitive inhibitors of HMG-CoA reductase with respect to the binding of the substrate, HMG-CoA, but not for that of the co-enzyme NADPH, suggesting that their HMG-CoA-like moieties bind to the HMG-CoA-binding portion of the enzyme active site. The structural mechanism for statin inhibition of HMG-CoA reductase has been elucidated by solving crystal structures of the catalytic portion of the enzyme bound to six different statins [25]. The structures revealed that statins act by binding to the active site of the enzyme, sterically preventing the substrate from binding. The

substrate-binding pocket of the enzyme also undergoes a rearrangement that enables the rigid, hydrophobic ring structures of the statins to be accommodated. Comparison of the six statin–enzyme complexes revealed subtle differences in their modes of binding. An additional hydrogen bond was demonstrated in the atorvastatin– and rosuvastatin–enzyme complexes along with a polar interaction unique to rosuvastatin, such that rosuvastatin has the most binding interactions with HMG-CoA reductase of all the statins. The full significance of these differences remains to be elucidated, but additional bonding properties of statins to the enzyme may account in part for increased potency.

PHARMACOKINETIC PROPERTIES OF STATINS

Lovastatin and simvastatin are administered as lactone pro-drugs, and are enzymatically hydrolysed in vivo to their active, hydroxy-acid form [26]. The other statins are administered as the active hydroxy acid [9,24,27]. Some key pharmacokinetic properties of the individual statins are summarized in *Table II*.

All statins are absorbed rapidly following administration, reaching peak plasma concentration (T_{max}) within 4 h [28–31]. The rate and extent of absorption of atorvastatin is affected by time-of-day administration [28], while pharmacokinetic properties of rosuvastatin are unaffected [32]; however, for both drugs, the lipid-lowering effects are similar whether administered in the morning or evening [28,32]. This is consistent with their long half-lives in comparison with the other approved statins, which have short elimination half-lives of 3 h or less [29,30,33] and are best administered in the evening, when the rate of endogenous cholesterol synthesis is highest. The elimination half-life of atorvastatin is approximately 14 h [28], a property that contributes to the drug's greater efficacy for lowering LDL-C compared with the older statins [34]; active metabolites of the atorvastatin parent compound extend the effect on HMG-CoA reductase and result in a half-life of enzyme inhibition of 20–30 h [35]. The elimination half-life of rosuvastatin is typically 19 h [31], while that of pitavastatin is 11 h [27]. The currently available statins generally possess a low systemic bioavailability, indicating extensive first-pass extraction [29,30,36,37]. The systemic bioavailability of cerivastatin is higher at 60% [38], and that of pitavastatin has been reported to be higher still, at approximately 80% [27]. Given that the liver is the target organ for statins, efficient first-pass

Table II Pharmacokinetic properties of the statins.

	Atorvastatin	Cerivastatin[a]	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin	Pitavastatin [Ref. 27]
Optimal time of dosing	Any time of day	Evening [Ref. 74]	Bedtime	With meals morning and evening	Bedtime	Evening	Any time of day	na
Bioavailability (%)	12	60 [Ref. 9]	24	5	18	5	20	~80
Solubility	Lipophilic	Lipophilic [Ref. 24]	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Lipophilic
Effect of food	Bioavailability decreased	No effect	Bioavailability decreased	Bioavailability increased	Bioavailability decreased	No effect	No effect	na
Protein binding (%)	98	>99 [Ref. 9]	>98	>95	~50	95–98	90	96
Active metabolites	✔	✔ [Ref. 9]	×	✔	×	✔	Minor	Minor
Elimination half-life (h)	14	2.5 [Ref. 9]	1.2	3	1.8	2	19	11
CYP450 metabolism and isoenzyme	✔ 3A4	✔ 3A4, 2C8 [Ref. 9]	✔ 2C9	✔ 3A4	×	✔ 3A4	Limited	Limited
Renal excretion (%)	<5	30 [Ref. 9]	6	10	20	13	10	na

[a]Voluntarily withdrawn from clinical use; na, not available.
Adapted from Rosenson [70].

uptake may be more important than high bioavailability for statin effect.

Food intake has a variable effect on statin absorption; lovastatin is more effectively absorbed when taken along with food [39], whereas the bioavailability of atorvastatin, fluvastatin and pravastatin is decreased [40–42]. No such effect is apparent for simvastatin or rosuvastatin [9,21]. However, the hypocholesterolaemic effect of the currently available statins does not appear to be affected by whether the drug is taken with the evening meal or at bedtime [39].

With the exception of pravastatin, all statins are extensively bound to plasma proteins (*Table II*), and as a result systemic exposure to unbound, pharmacologically active drug is relatively low [9]. Although circulating levels of unbound pravastatin are high relative to those of the other statins, widespread tissue distribution is prevented by the hydrophilic nature of the drug [43]. As previously described, rosuvastatin is comparably hydrophilic to pravastatin, whereas the other statins are lipophilic in nature; cerivastatin has the highest octanol-water coefficient indicating the greatest degree of lipophilicity [9,24]. All statins are relatively hepatoselective with respect to inhibition of HMG-CoA reductase, an important property given that the majority of endogenous cholesterol production occurs in the liver. The mechanisms contributing to this hepatoselective effect are governed by the solubility profile of the statin. For lipophilic statins, passive diffusion through hepatocyte cell membranes is primarily responsible for efficient first-pass uptake, while for hydrophilic statins extensive carrier-mediated uptake is the major mechanism [43,44]. While lipophilicity results in efficient hepatic shunting, the same property will result in ready passage through nonhepatic cell membranes. This contributes to the fact that hydrophilic statins exhibit greater hepatoselectivity. Indeed, the lack of influence of pravastatin on smooth muscle cell proliferation is likely to be due to low penetration of the cells by the drug [45]. A recent study has examined the uptake of rosuvastatin and pravastatin by rat hepatocytes [44]. The study demonstrated that rosuvastatin and pravastatin are taken up by hepatocytes by a high-affinity process, with the transport efficiency for rosuvastatin higher than that of pravastatin.

Statins are predominantly metabolized by the cytochrome P_{450} (CYP450) family of enzymes, composed of over 30 isoenzymes [46]. The CYP3A4 isoenzyme metabolizes the greatest number of drugs in humans [47], including lovastatin, simvastatin and atorvastatin [46]. A proportion of the circulating inhibitory activity of these three agents for HMG-CoA reductase is attributable to active metabolites. For atorvastatin, the major active metabolites are 2-hydroxy- and 4-hydroxy-atorvastatin acid [48], while for simvastatin the β-hydroxy acid and its 6′-hydroxy, 6′-hydroxymethyl and 6′-exomethylene derivatives are the major active metabolites [49,50]. Fluvastatin is chiefly metabolized by the CYP2C9 isoenzyme, while pravastatin, pitavastatin and rosuvastatin do not undergo substantial metabolism by CYP450 pathways [46,51,52]. Lipophilic drugs are known to be much more susceptible to oxidative metabolism by the CYP450 system [53]. It is now recognized that the statins metabolized by the CYP450 system are more likely to produce muscle toxicity because of the risk of drug interactions with many drugs that inhibit CYP450, notably the CYP3A4 isoform [54,55]; drug interactions may increase plasma levels of statins, with a consequent increased risk of toxic effects.

The predominant route of elimination for the majority of statins is via the bile after metabolism by the liver [56]. Consequently, hepatic dysfunction is a risk factor for statin-induced myopathy [4], and all manufacturers recommend caution when prescribing statins to patients with a history of liver disease. Pravastatin is eliminated by both the kidney and liver, mostly as unchanged drug [33,57]. However, as with some of the other currently available statins, its pharmacokinetics are altered in patients with hepatic dysfunction [39]. Rosuvastatin is also eliminated, largely unchanged, by both the kidney and liver [37,58], and its pharmacokinetic properties are not altered in patients with mild to moderate hepatic impairment [59].

EFFICACY AND SAFETY OF STATINS

Statins are highly efficacious at lowering LDL-C, although there are differences in the extent of LDL-C lowering at therapeutic doses and in the maximal reduction achieved with each agent (*Table I*). Of the statins currently available, rosuvastatin is the most effective at lowering LDL-C, with reductions of up to 63% reported with a daily dose of 40 mg [60]. Data from comparative trials confirm that on a milligram basis, rosuvastatin is the most efficacious statin for lowering LDL-C, followed by atorvastatin, simvastatin and pravastatin [61,62]. Pitavastatin (2 mg/day) has been shown to reduce total cholesterol and LDL-C concentrations by 28 and 38%, respectively [63], and the lipid-modifying efficacy of pitavastatin was considered to be

similar to that of atorvastatin [27]. Statins also increase HDL-C levels to varying degrees, although a predictable dose–response relationship is not always observed. In a comparative study in patients with hypercholesterolaemia, rosuvastatin 10–40 mg increased HDL-C by 7.7–9.6%, compared with 2.1–5.7% for atorvastatin 10–80 mg, 5.2–6.8% for simvastatin 10–80 mg, and 3.2–5.6% for pravastatin 10–40 mg [62].

The effect of atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin on inhibition of cholesterol synthesis has been compared in primary rat hepatocytes. Rosuvastatin exhibited a 50% inhibitory concentration (IC_{50}) of 0.16 nM and was significantly more potent than the other statins investigated, with IC_{50}s ranging from 1.16 nM (atorvastatin) to 6.93 nM (pravastatin) [24]. The more potent inhibition of hepatic cholesterol synthesis by rosuvastatin explains its greater efficacy for lowering LDL-C [21]. Limited data are available on the relative potency of pitavastatin, although a study in isolated rat liver microsomes reported that pitavastatin was 2.4- and 6.8-fold more potent than simvastatin and pravastatin, respectively, with an IC_{50} of 6.8 nM [27].

In general, statins are well tolerated and serious adverse events are rare [64]. The most serious adverse effect associated with statin therapy is myopathy, which may progress to fatal or nonfatal rhabdomyolysis. The withdrawal of cerivastatin from clinical use in 2001 heightened scrutiny of these effects, although all available data indicate that the increased incidence of rhabdomyolysis reported for cerivastatin appears to be specific to this agent [20,65]. The incidence of myopathy is low (approximately one in 1000 patients treated), is dose-related, and is increased when statins are used in combination with agents that share common metabolic pathways [66]. A recent analysis of data from clinical trials supports a low incidence of severe muscle problems with statin therapy [67]. Among 83 858 patients randomly assigned to a statin or placebo in a total of 30 studies, 49 cases of myositis (defined either by study investigators or as creatinine kinase elevation >10 times the upper limit of normal) and seven cases of rhabdomyolysis were reported in the statin groups ($n = 42\ 323$) compared with 44 and five cases, respectively, in the placebo groups ($n = 41\ 535$).

Assessments of safety derived from the clinical development programmes for atorvastatin and rosuvastatin reiterate that statins are generally safe and well tolerated [68,69]. Newman et al. [68] analysed pooled data from 44 clinical trials of atorvastatin, completed as of November 2001, involving 16 495 patients. Withdrawal because of treatment-associated adverse events was low for patients receiving atorvastatin (3%, $n = 9416$) and other statins (4%, $n = 5290$). Treatment-associated serious adverse events were rare and reported in <1% of patients in both the atorvastatin and other statin groups, and no deaths were considered related to treatment. In the clinical trial programme of rosuvastatin, reviewed as of April 2003, adverse events leading to treatment withdrawal occurred in 2.9% of patients receiving rosuvastatin 10–40 mg ($n = 3074$) and 2.9% of patients receiving atorvastatin 10–80 mg, simvastatin 10–80 mg or pravastatin 10–40 mg ($n = 5634$) [69,70]. In this programme, proteinuria was observed in a small number of patients receiving statin therapy [69]. These findings of proteinuria were mostly transient and reversible, and not associated with long-term detrimental effects on renal function [69]. Interestingly, recent in vitro studies with rosuvastatin, atorvastatin, simvastatin, and pravastatin demonstrated that inhibition of HMG-CoA reductase in proximal tubule cells reduced the rate of renal tubular protein re-absorption, suggesting a potential pharmacological mechanism for the proteinuria seen with statin therapy [71,72].

CONCLUSION

Statins are highly effective cholesterol-lowering agents, and have been shown to reduce cardiovascular morbidity and mortality in patients with and without CHD. Consequently, statins have become the therapy of choice for the treatment of many dyslipidaemias. Seven statins are currently approved for clinical use in at least one country. Although they share a common mechanism of action, there are differences in their relative efficacy for improving the lipid profile, as well as in their chemistry and pharmacokinetics. Consideration of these differences should help to provide a rational basis for the safe and effective use of the current and emerging statins in clinical practice.

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