Clin. Cardiol. Vol. 26 (Suppl. III), III-32–III-38 (2003)

Pharmacologic Characteristics of Statins

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Summary: Considerable effort has been devoted to improving the pharmacologic characteristics and clinical effects of statins. Desirable pharmacologic properties include potent inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, selectivity of uptake in hepatocytes, low systemic bioavailability to reduce systemic adverse effects, prolonged elimination half-life, and no or minimal hepatic metabolism to avoid drug–drug interactions. The desirable effects on lipid variables would include increased effectiveness in reducing levels of low-density lipoprotein cholesterol and other atherogenic lipoproteins and measurable beneficial effects on high-density lipoprotein cholesterol levels. As a product of the ongoing efforts regarding statin pharmacology, the new statin rosuvastatin exhibits significant improvements in several of these characteristics.

Key words: statins, pharmacology, low-density lipoprotein cholesterol, rosuvastatin

Introduction

Statins are the drugs of first choice for management of many lipid disorders. These drugs share many features, but also exhibit differences in pharmacologic attributes that may contribute to differences in clinical utility and effectiveness in modifying lipid risk factors for coronary heart disease. Some of the features desired with statin therapy include potent reversible inhibition of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the ability to produce large reductions in low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), the ability to increase HDL cholesterol (HDL-C), tissue selectivity (which focuses on treatment effects), optimal pharmacokinetics that limits systemic bioavailability and offers once a day dosing, and a low potential for drug–drug interactions.

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Inhibition of Hydroxymethylglutaryl Coenzyme A Reductase

All statins interfere with the conversion of HMG-CoA to the cholesterol precursor mevalonate by HMG-CoA reductase, an early and rate-limiting step in cholesterol synthesis. Statins competitively inhibit HMG-CoA reductase by binding to the enzyme and sterically inhibiting substrate binding. The degree of inhibition exhibited by statin compounds may differ depending on the strength of their bond to the enzyme.

Recent molecular studies have provided insights into the binding characteristics of statin molecules with HMG-CoA reductase.[1] All of the statin molecules contain an HMG-like moiety that binds to the catalytic domain of the target enzyme. In addition, the base structures of these compounds determine how well the molecule fits into the binding pocket of the enzyme and binds with it. The synthetic statins, including cerivastatin, fluvastatin, atorvastatin, and rosuvastatin (currently in development), contain a fluorinated phenol group and other moieties in the base structure that provide additional sites for binding within the enzyme pocket.

X-ray crystallography of statin-HMG-CoA reductase complexes has allowed visualization of these binding characteristics (Fig. 1). Through this work, it has been shown that all statins bind with the enzyme through van der Waals forces with the HMG-like moiety and the base structure (approximately eight such bonds).

The synthetic statins have, in addition, a polar interaction via their fluorinated phenol group. Both atorvastatin and rosuvastatin form an additional hydrogen bond with the Ser^{565} residue in the enzyme and the carbonyl oxygen of atorvastatin or the sulfone oxygen of rosuvastatin. Rosuvastatin exhibits an additional and unique polar interaction between its sulfone group and the enzyme Arg^{568} side chain in the enzyme. These studies show that rosuvastatin has the greatest number of binding interactions with the enzyme active site and that both rosuvastatin and atorvastatin have an additional interaction with the enzyme that is not seen with the other synthetic statins. These differences in the number and types of bonds between the statin and enzyme may explain the relatively greater efficacy of atorvastatin and rosuvastatin to lower LDL-C.

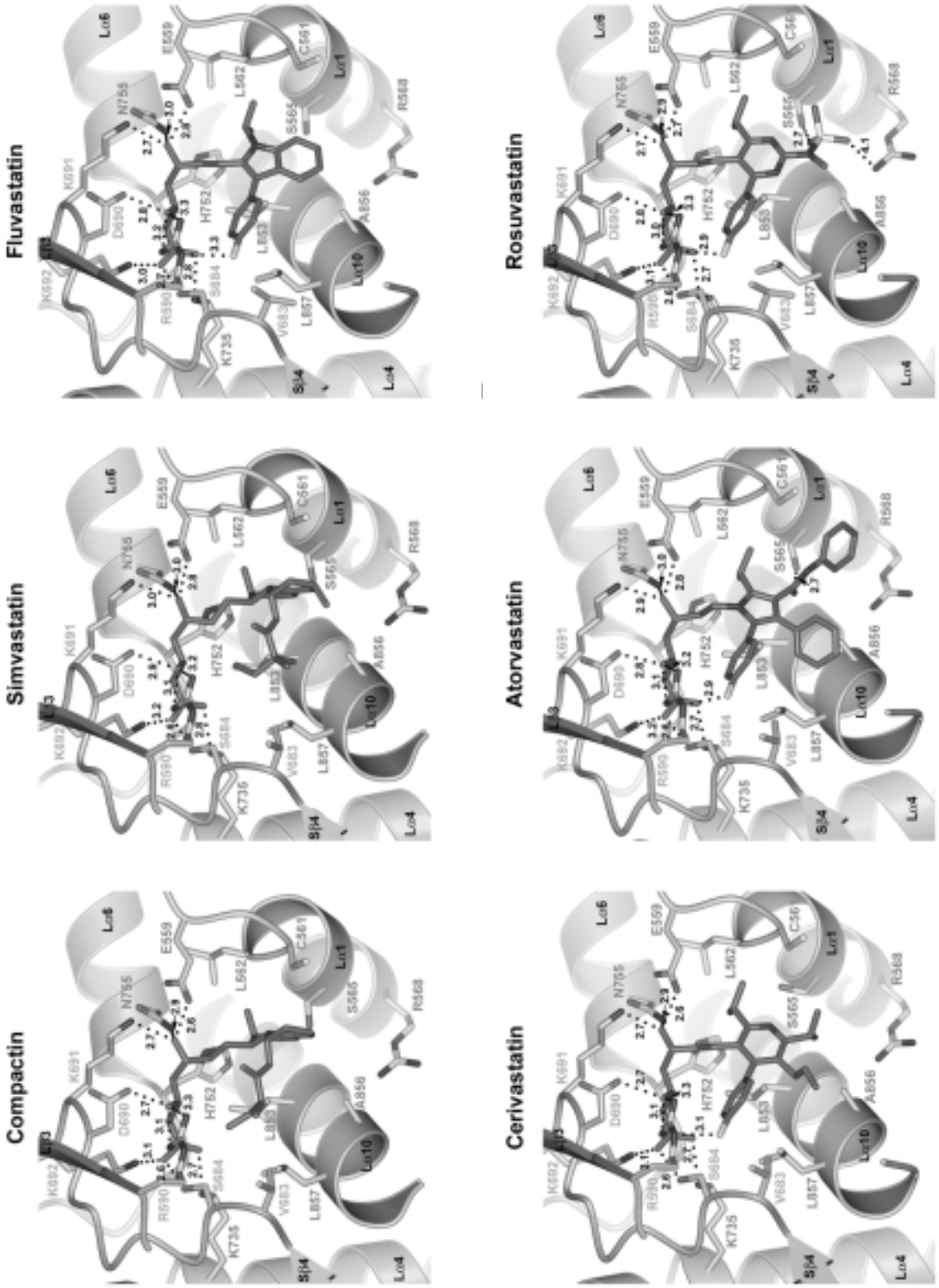

FIG. 1 Statin-HMG-CoA reductase complexes showing binding characteristics. Both rosuvastatin and atorvastatin form an additional hydrogen bond with the enzyme Ser^{565} residue, with binding occurring through the rosuvastatin sulfone oxygen atom or the atorvastatin carbonyl oxygen atom. In addition, rosuvastatin exhibits a unique polar interaction between its sulfone group and the enzyme Arg^{568} side chain. Adapted from Ref. No. 1.

The theory that greater binding to the enzyme translates into greater potency of the statin appears to be confirmed in in vitro and in vivo studies. Studies in purified human HMG-CoA reductase catalytic domain preparations[2,3] showed that rosuvastatin's ability to inhibit 50% of HMG-CoA reductase activity occurs at the lowest concentration (IC_{50} = 5.4 nM) among the statins tested, followed by atorvastatin (8.2 nM) (Fig. 2). Similar findings were made in a study of primary rat hepatocytes;[3,4] mean IC_{50} values for inhibition of cholesterol synthesis in this model were 0.16 nM for rosuvastatin, 1.16 nM for atorvastatin, 2.74 nM for simvastatin, 3.54 nM for cerivastatin, 3.78 nM for fluvastatin, and 6.93 nM for pravastatin.

Effects on Non-High-Density Lipoprotein Cholesterol and High-Density Lipoprotein Cholesterol

The reduction in cholesterol synthesis with statin therapy causes a reduction in intracellular cholesterol concentrations and a subsequent upregulation of hepatocyte LDL receptors. These receptors recognize and bind with apolipoproteins B and E on the surface of circulating very-low-density lipoprotein (VLDL) and LDL particles, resulting in uptake and degradation by the cells. Some statins, especially those with greater potency, also lower circulating VLDL and LDL levels by reducing the secretion of VLDL and VLDL-like lipoproteins from the liver, thus reducing the quantities of lipoprotein available to serve as substrate for conversion to atherogenic remnant particles (Fig. 3).

Common forms of dyslipidemia encountered in the clinical setting include hypercholesterolemia characterized by marked elevation of LDL-C (with or without decreased HDL-C) and mixed dyslipidemia that is characterized by elevated triglyceride and LDL-C levels. In the case of mixed dyslipidemia, large quantities of cholesterol may be carried by triglyceride-rich VLDL, intermediate-density lipoproteins (IDL), and LDL particles. A greatly increased number of small LDL particles that accumulate via a prolonged residence of lipoproteins in the circulation are also frequently present. In addition, there is an increase in the number (concentration) of atherogenic VLDL and LDL particles in these patients, which many experts believe is the key factor accounting for the increased risk of CHD.

To focus attention on the need to reduce levels of atherogenic remnant particles in these cases, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) has introduced the measure of non-HDL-C as a secondary treatment target in patients with elevated triglyceride levels after achieving recommended LDL-C targets.[5] Since non-HDL-C includes LDL-C (which includes IDL and small, dense LDL particles) as well as VLDL remnant particles, it serves as a measure of all atherogenic lipoproteins. It has therefore become important to assess the effects of lipid-altering drugs in reducing non-HDL-C.

In most cases, non-HDL-C goals are achieved when LDL-C goals are achieved. In cases where non-HDL-C levels remain high after LDL-C goals are achieved, one option is to use statins in doses beyond those required to achieve the LDL-C goal. A recent analysis of data from the Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS),[6] performed in patients with elevated LDL-C, examined the effects of atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin on non-HDL-C levels when doses of these drugs were titrated to achieve NCEP LDL-C goals. The reductions in non-HDL-C levels were very similar to the reductions in LDL-C levels, with the percentage reductions in non-HDL-C being just a few percent (i.e., 2–4%) less than reductions achieved in LDL-C for each treatment group. The most potent LDL-C-lowering statin was also the most potent non-HDL-C-lowering statin. Atorvastatin lowered LDL-C and non-HDL-C more (42 and 38%, respectively) than the other statins studied (29 and 26% for fluvastatin, 36 and 32% for lovastatin, 28 and 26% for pravastatin, and 36 and 32% for simvastatin, respectively).

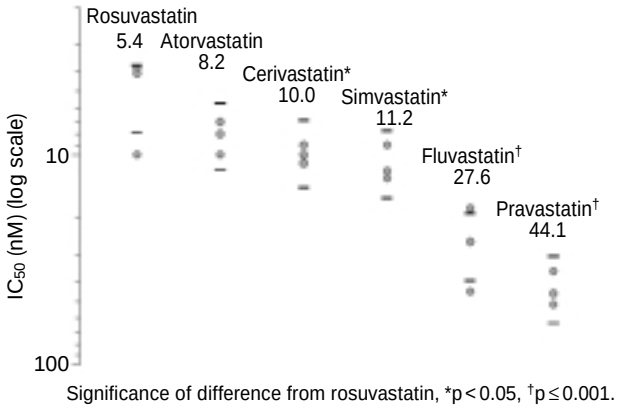

FIG. 2 Inhibition of purified human hydroxymethylglutaryl coenzyme A reductase catalytic domain by statins. Among the statins tested, rosuvastatin had the lowest 50% inhibitory concentration, followed by atorvastatin. Reproduced from Ref. No. 2 with permission.

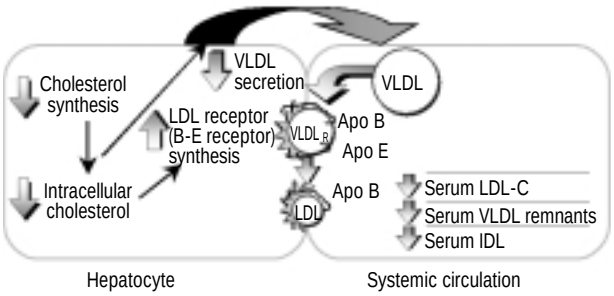

FIG. 3 Schematic representation of statin mechanism of action. Statins reduce hepatic cholesterol synthesis, lower levels of intracellular cholesterol, stimulate upregulation of the low-density lipoprotein (LDL) receptor, and increase uptake of non-high-density lipoprotein particles from the systemic circulation. Apo = apolipoprotein, IDL = intermediate-density lipoprotein, LDL-C = low-density lipoprotein cholesterol, VLDL = very-low-density lipoprotein.

Rosuvastatin has been shown to reduce LDL-C levels significantly more than atorvastatin and other statins at starting doses and when doses were titrated to achieve NCEP goal levels.[7–10] Comparison of the effect of doses of rosuvastatin 5 mg and 10 mg with atorvastatin 10 mg in hypercholesterolemic patients at 12 weeks revealed that both groups treated with rosuvastatin achieved significantly greater reductions in both LDL-C and non-HDL-C than did the atorvastatin group.[8] After an additional 40 weeks in which doses could be sequentially doubled if necessary to meet NCEP ATP II goals, treatment with rosuvastatin remained significantly superior to atorvastatin at 52 weeks in terms of change from baseline in LDL-C and non-HDL-C (Fig. 4). Moreover, rosuvastatin enabled more patients to achieve NCEP ATP II goals for LDL-C lowering, compared with atorvastatin.

As for the best way to manage patients with increased levels of small, dense LDL, the traditional approach has been to utilize niacin because it appears to lower these levels and shifts patients from the more atherogenic pattern B to the less atherogenic pattern A phenotype. Recent research with statins calls this approach into question. One study assessed the effects of atorvastatin and niacin on LDL subfractions in patients with elevated levels of total cholesterol, triglycerides (200 to 800 mg/dl), and apolipoprotein B.[11] Atorvastatin 10 mg reduced LDL-C overall by 28%, compared with a 7% reduction with niacin 3 g (patients actually took an average of 2,116 mg daily in this study) (Fig. 5). The predominant effect of niacin was a shift in subfractions from small, dense LDL to large LDL (from LDL phenotype B to phenotype A). The primary effect of atorvastatin was a substantial reduction in small, dense LDL particles, small reductions in other LDL subfractions, and a superior overall reduction in LDL-C.

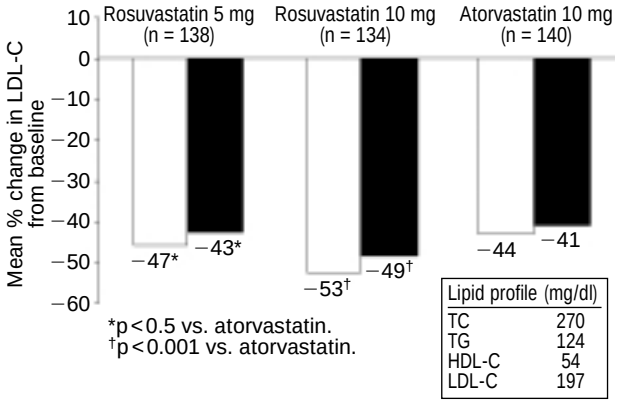

FIG. 4 Effects of rosuvastatin and atorvastatin at 52 weeks. In these hypercholesterolemic patients, starting doses of rosuvastatin 5 mg and 10 mg and atorvastatin 10 mg remained fixed for 12 weeks, after which doses could be titrated to achieve the Second National Cholesterol Education Project Adult Treatment Panel (ATP II) goals for reducing low-density lipoprotein cholesterol (LDL-C). Both rosuvastatin groups demonstrated significantly superior reductions in LDL-C compared with the atorvastatin group. HDL-C = high-density lipoprotein cholesterol, TC = total cholesterol, TG = triglycerides. □ = LDL-C, ■ = non-HDL-C.

Another study that assessed the effects of rosuvastatin 40 mg on lipoprotein subfractions in patients with elevated triglyceride levels (> 2.0 mmol/l, > 180 mg/dl) also showed significant reductions in small, dense LDL (LDL III) concentrations (from 165 to 62 mg/dl) and in remnant lipoprotein cholesterol (from 10.6 to 6.3 mg/dl).[12] These findings have now been confirmed by others.[13–15] Based on these results, many authorities now advocate the use of potent statins in patients with mixed dyslipidemia (i.e., the metabolic syndrome) to achieve a substantial reduction in small, dense LDL particles as well as in the overall LDL-C and non-HDL-C levels and the total number of atherogenic particles.

High-Density Lipoprotein Cholesterol

Statins generally produce modest increases in HDL-C. One mechanism whereby statins may increase HDL-C is through increasing production of apolipoprotein A-I (the major apolipoprotein in HDL) and thus nascent HDL. The HMG-CoA reductase inhibition may lead to an increase in HDL-C by producing a reduction of downstream farnesyl pyrophosphate production, inducing upregulation of PPARα receptors in the periphery and consequently increasing apolipoprotein A-I production. A second potential mechanism for increasing HDL-C is a reduction in transfer of cholesteryl esters from HDL to VLDL and LDL particles via inhibition of cholesteryl ester transfer protein.

Tissue Selectivity

Differences among statins in relative lipophilicity or hydrophilicity may influence drug kinetics and tissue selectivity. Compared with other statins, pravastatin and rosuvastatin exhibit relatively low lipophilicity. In the case of rosuvastatin, this property is conferred by the presence of a polar methane sulfonamide group on the drug molecule. In a study assessing

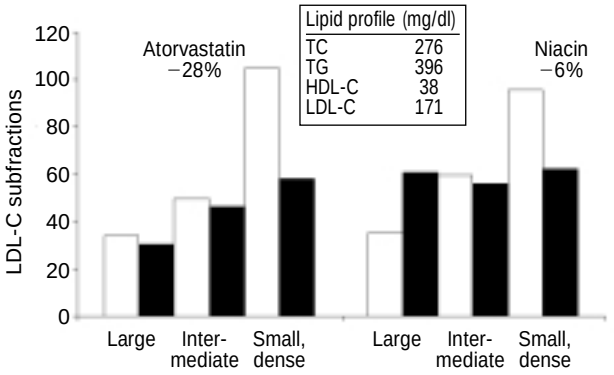

FIG. 5 Effect of atorvastatin 10 mg and niacin on low-density lipoprotein cholesterol (LDL-C) subfractions in patients with atherogenic dyslipidemia. Abbreviations as in Figure 4. □ = Baseline, ■ = treatment. Data are from Ref. No. 11.

lipophilic/hydrophilic characteristics of a number of statins, the statin octanol-water coefficients were −0.84 log D at pH 7.4 for pravastatin and −0.33 log D for rosuvastatin, compared with values of 1.0 to 2.0 for atorvastatin, fluvastatin, simvastatin, and cerivastatin, indicating greater lipophilicity on the part of these latter drugs (Fig. 6).[2, 16] Lipophilic drugs exhibit greater diffusion into most cell lines, whether hepatic cells or peripheral cells. Relatively hydrophilic drugs may exhibit reduced access to nonhepatic cells as a result of low passive diffusion and increased relative hepatic cell uptake through selective organic ion transport. In addition, the relative water solubility of a drug may reduce the need for extensive cytochrome P450 (CYP) enzyme metabolism (see below). Compared with cultured fibroblasts, study of tissue selectivity with rosuvastatin showed a 1,000-fold increase in HMG-CoA reductase inhibitory effect in primary rat hepatocytes.[2, 4] When expressed as a log ratio of IC_{50} values in the two cell types, rosuvastatin and pravastatin exhibited ratios of 3.3, indicating divergent effects on HMG-CoA reductase inhibition in the two cell lines. By comparison, the log ratio of IC_{50} values with the two statins with the greatest lipophilicity, simvastatin and cerivastatin, were significantly lower values of 0.54 and −0.14, respectively (Fig. 6); values for fluvastatin and atorvastatin were −0.04 and 2.2, respectively. Additional studies[17] showed that the rate of active uptake clearance in rat hepatocytes was significantly greater for rosuvastatin than for pravastatin; both rosuvastatin and pravastatin exhibited liver-selective uptake after administration of intravenous drug in rats, whereas simvastatin exhibited high rates of uptake in both liver and such other tissues as the adrenals and spleen. The clinical significance of these findings remains to be demonstrated.

Pharmacokinetic Characteristics

Two of the more important pharmacokinetic variables for statins are bioavailability and elimination half-life. The implications of differences in systemic bioavailability of statins are not completely clear. Perhaps, in the ideal scenario, statin effects would be confined to the liver, with limited systemic availability and consequently a reduced risk of systemic adverse effects. However, some systemic availability may be required so that the pleiotropic effects can be observed in the vasculature with statin treatment. However, on balance, keeping the systemic availability of the statin to a minimum would appear to be desirable, particularly for more potent inhibitors, since a reduced systemic drug exposure would be expected to translate into a reduced inhibition of HMG-CoA reductase in nonhepatic cells and fewer associated adverse events. In this respect, it is of interest that cerivastatin, which has been removed from the market because of an unacceptable frequency of severe muscle toxicity, exhibits 60% systemic bioavailability, the greatest among the statins; in comparison, bioavailability is 24% for fluvastatin, ~ 20% for rosuvastatin, 17% for pravastatin, ~ 14% for atorvastatin, and < 5% for simvastatin (Table I).

Elimination half-life may be an important determinant of the relative LDL-C-lowering effectiveness of the statins together with the specific inhibitory effect on HMG-CoA reductase. Some authorities have posited that the longer the statin is available in suitable concentrations, the longer it inhibits HMG-CoA reductase and thus the greater it lowers LDL-C. Supporting this is the observation that atorvastatin (14 h) and rosuvastatin (20 h)[18] exhibit a markedly prolonged elimination half-life compared with other statins (2 to 3 h for cerivastatin, 1 to 2 h for simvastatin, pravastatin, and fluvastatin), and also have the most substantial LDL-C-lowering efficacy (Table I).

Potential for Drug–Drug Interactions

Many drugs, including several statins, are metabolized via the CYP 3A4 enzyme system, presenting a significant potential for drug–drug interactions when statins are used to reduce the risk of coronary heart disease. All statins except pravastatin are metabolized to some degree by CYP systems.[19, 20]

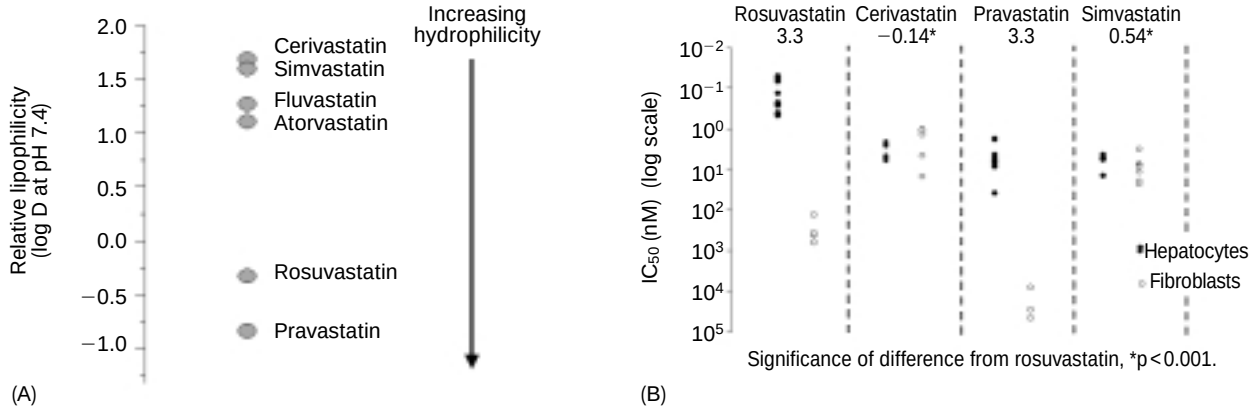

FIG. 6 (A) Relative lipophilicity/hydrophilicity of statins given as statin octanol-water coefficients (log D at pH 7.4).[2, 16] (B) Log ratios of hydroxymethylglutaryl coenzyme A reductase inhibition for hepatocytes:fibroblasts among statins.[2, 4] Adapted from Ref. No. 2.

TABLE I Summary: Pharmacologic properties of statins.

	IC_{50} (nM) for HMG-CoA reductase inhibition	Cell selectivity log ratio (hepatocyte: fibroblast)	Bioavailability (%)	Elimination half-life (h)	CYP 3A4 metabolism
Rosuvastatin	5.4	3.3	~20	20	No
Atorvastatin	8.2	2.2	~14	14	Yes
Cerivastatin	10.0	−0.14	60	2–3	Yes
Simvastatin	11.2	0.54	<5	1–2	Yes
Fluvastatin	27.6	−0.04	24	1–2	No
Pravastatin	44.1	3.3	17	1–2	No

Data from Refs. No. 2, 3, and 20.
Abbreviation: HMG-CoA = hydromethylglutaryl coenzyme A.

Lovastatin, simvastatin, atorvastatin, and cerivastatin undergo CYP 3A4 metabolism. Cerivastatin is also metabolized via the CYP 2C8 system, whereas fluvastatin is metabolized only via the CYP 2C9 enzymes, and a small amount of rosuvastatin undergoes metabolism (at most 10%) via the CYP 2C9 system.[21] Pravastatin is metabolized by sulfation or other mechanisms.

Drugs that inhibit CYP 3A4 may increase systemic statin concentrations, which increases the risk of drug toxicity, whereas substrates for the enzyme system may also increase systemic statin concentrations by competing with the statin for the same metabolic pathway. A partial listing of inhibitors and substrates for the CYP 3A4 system is shown in Table II.[19, 20] Among the CYP 3A4 inhibitors are the antifungal agents itraconazole and ketoconazole, cyclosporine, macrolide antibiotics, HIV-protease inhibitors, and grapefruit juice. Inhibitors of CYP 2C9 also include azole antifungals, as well as cimetidine. In the case of itraconazole, for example, coadministration with statins results in increases in the statin area under the concentration-time curve of 15-fold for lovastatin,[22] 19-fold for simvastatin,[23] 3-fold for atorvastatin,[24] 1.7-fold for pravastatin,[23] but only 1.3-fold for fluvastatin[22] and rosuvastatin.

Product information for lovastatin, pravastatin, and simvastatin indicate that area under the curve (AUC) values for these drugs are significantly increased (3- to 20-fold) when they are used in combination with gemfibrozil.[25, 26] The mechanism of this interaction is unknown. The package insert for fluvastatin indicates the absence of an interaction with gemfibrozil. It is unknown whether such an interaction occurs with atorvastatin, and no data on such a potential interaction with rosuvastatin have yet been reported. The combination of any statin with fenofibrate does not appear to result in a change in the statin's AUC.

TABLE II Partial listing of CYP 3A4 inhibitors and substrates

• Inhibitors	• Substrates
Nefazodone	Quinidine
Fluvoxamine	Carbamazepine
Ketoconazole	Nefazodone
Itraconazole	Benzodiazepines
Cyclosporine	Calcium-channel blockers
Erythromycin	Cyclosporine
Clarithromycin	Nonsedating antihistamines
Sertraline	Sertraline
HIV-protease inhibitors	Lovastatin, simvastatin,
Grapefruit juice	atorvastatin

Data from Refs. No. 19 and 20.

Conclusion

Desirable pharmacologic properties of a statin include potency in inhibiting HMG-CoA, selectivity of effect or uptake in hepatic cells to increase inhibitory activity and reduce activity in nonhepatic cells, lower systemic bioavailability to minimize systemic adverse effects, prolonged elimination half-life, and absence of or minimal metabolism via the CYP 3A4 system. The characteristics of statins in these areas are summarized in Table I. Among the statins, rosuvastatin would appear to have the most favorable overall profile, at least with regard to the features considered in this paper. In terms of modifying lipid profiles, rosuvastatin produces the greatest reductions in LDL-C and non-HDL-C, as might be predicted from the drug's pharmacologic profile, and the greatest increases in HDL-C compared with other marketed statins.

References

1. Istvan ES, Deisenhofer J: Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–1164
2. McTaggart F, Buckett L, Davidson R, Holdgate G, McCormick A, Schneck D, Smith G, Warwick M: Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol* 2001;87(suppl):28B–32B
3. Chapman MJ, McTaggart F: Optimizing the pharmacology of statins: Characteristics of rosuvastatin. *Atheroscler Suppl* 2002;2: 33–37
4. Buckett L, Ballard P, Davidson R, Dunkley C, Martin L, Stafford J, McTaggart F: Selectivity of ZD4522 for inhibition of cholesterol synthesis in hepatic versus nonhepatic cells (abstr). *Atherosclerosis* 2000;151:41

5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *J Am Med Assoc* 2001;285:2486–2497
6. Ballantyne CM, Andrews TC, Hsia JA, Kramer JH, Shear C: Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: Effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. *Am J Cardiol* 2001;88:265–269
7. Davidson M, Ma P, Stein EA, Gotto AM Jr, Raza A, Chitra R, Hutchinson HG: Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. *Am J Cardiol* 2002; 89:268–275
8. Olsson AG, Istad H, Luurila O, Ose L, Stender S, Tuomilehto J, Wiklund O, Southworth H, Pears J, Wilpshar JW, on behalf of the Rosuvastatin Investigators Group: Effects of rosuvastatin and atorvastatin compared over 52 weeks of treatment in patients with hypercholesterolemia. *Am Heart J* 2002;144:1044–1051
9. Paoletti R, Fahmy M, Mahla G, Mizan J, Southworth H: Rosuvastatin demonstrates greater reduction of low-density lipoprotein cholesterol compared with pravastatin and simvastatin in hypercholesterolemic patients: A randomized, double-blind study. *J Cardiovasc Risk* 2001;8:383–390
10. Brown WV, Chitra RR, Zedler BK, Bays HE, Hassman HA: Long-term efficacy and safety of rosuvastatin: Results of a 52-week comparator-controlled trial versus pravastatin and simvastatin (abstr P1526). *Eur Heart J* 2001;22(suppl):270
11. McKenney JM, McCormick LS, Schaefer EJ, Black DM, Watkins ML: Effect of niacin and atorvastatin on lipoprotein subclasses in patients with atherogenic dyslipidemia. *Am J Cardiol* 2001;88: 270–274
12. Caslake MJ, Stewart G, Day S, Daly E, Nwose OM, Chapman MJ, Durrington P, Laggner P, Pears J, Packard CJ: Rosuvastatin normalises atherogenic levels of apoB-containing lipoprotein subfractions (abstr). *Int J Clin Pract* 2002;suppl 124:8
13. Sasaki S, Kuwahara N, Kunitomo K, Harada S, Yamada T, Azuma A, Takeda K, Nakagawa M: Effects of atorvastatin on oxidized low-density lipoprotein, low-density lipoprotein subfraction distribution, and remnant lipoprotein in patients with mixed hyperlipidemia. *Am J Cardiol* 2002;89:386–389
14. Miller M, Dolinar C, Cromwell W, Otvos JD: Effectiveness of high doses of simvastatin as monotherapy in mixed hyperlipidemia. *Am J Cardiol* 2001;87:232–234
15. Rosenson R, Otvos JD, Freedman DS: Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-1) trial. *Am J Cardiol* 2002;90: 89–94
16. Smith G, Davidson R, Bloor S, Burns K, Calnan C, McAulay P, Torr N, Ward W, McTaggart F: Pharmacological properties of ZD4522—a new HMG-CoA reductase inhibitor (abstr). *Atherosclerosis* 2000;151:39
17. Nezasa K, Higaki K, Hasegawa H, Inazawa K, Takeuchi M, Yukawa T, McTaggart F, Nakano M: Uptake of HMG-CoA reductase inhibitor ZD4522 into hepatocytes and distribution into liver and other tissues of the rat (abstr). *Atherosclerosis* 2000;151:39
18. Warwick MJ, Dane AL, Raza A, Schneck DW: Single- and multiple-dose pharmacokinetics and safety of the new HMG-CoA reductase inhibitor ZD4522 (abstr). *Atherosclerosis* 2000;151:39
19. Bottorff M, Hansten P: Long-term safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors. *Arch Intern Med* 2000; 160:2273–2280
20. Beaird SL: HMG CoA reductase inhibitors: Assessing differences in drug interactions and safety profiles. *J Am Pharm Assoc* 2000; 40:637–644
21. McCormick AD, McKillop D, Bulters CJ, Miles GS, Baba T, Touchi A, Yamaguchi Y: ZD4522: An HMG-CoA reductase inhibitor free of metabolically mediated drug interactions: Metabolic studies in human in vitro systems (abstr). *J Clin Pharmacol* 2000; 40:1055
22. Kivisto KT, Kantola T, Neuvonen PJ: Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998;46:49–53
23. Neuvonen PJ, Kantola T, Kivisto KT: Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998;63:332–341
24. Kantola T, Kivisto KT, Neuvonen PJ: Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998;64: 58–65
25. Kyrklund C, Backman JT, Kivisto KT, Neuvonen M, Laitila J, Neuvonen PJ: Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001;69:340–345
26. Backman JT, Kyrklund C, Kivisto KT, Wang JS, Neuvonen PJ: Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000;68:122–129