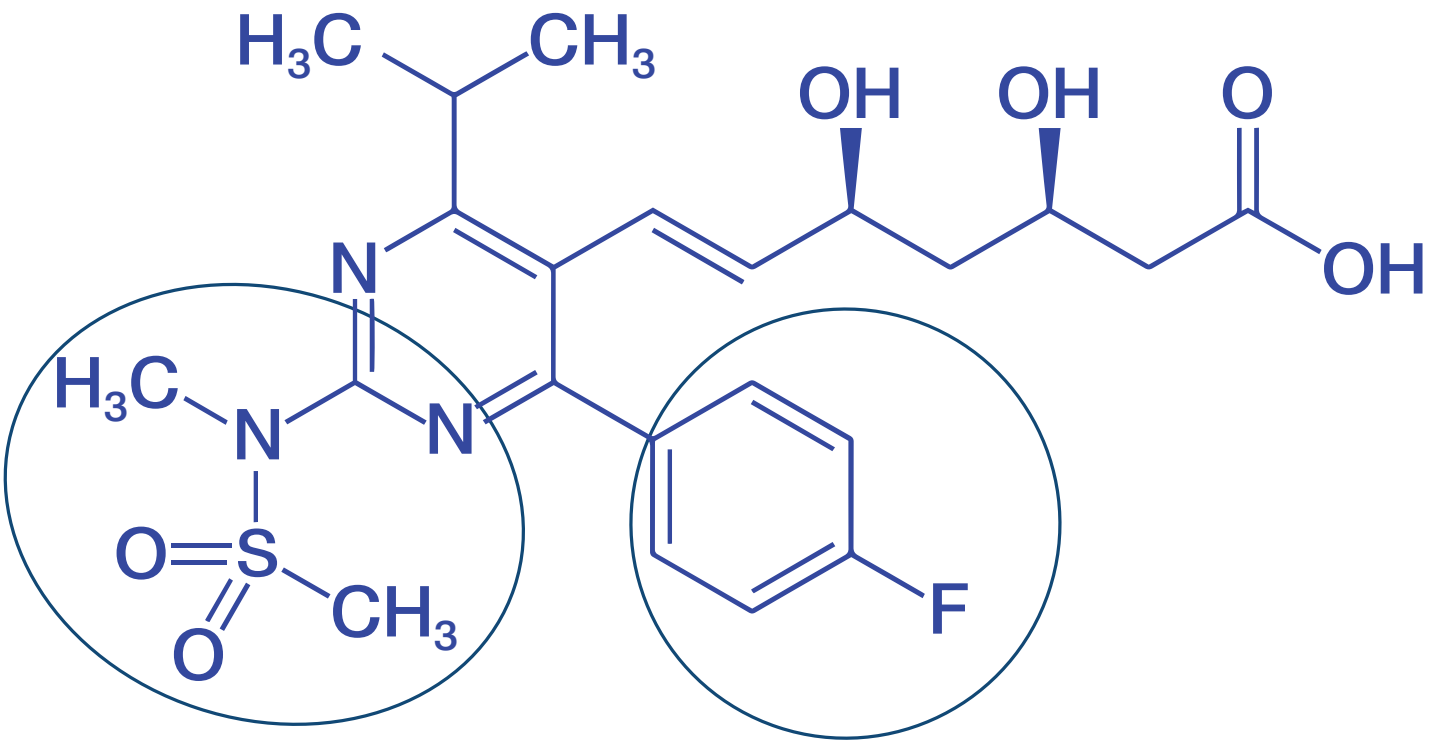

Polar Methane Sulphonamide group

Fluorinated Phenyl group

Rosuvastatin

Rosumax

Rosuvastatin BP 5 mg, 10 mg & 20 mg Tablet

A Preparation of COS Grade Rosuvastatin

Rosumax

Rosuvastatin BP 5 mg, 10 mg & 20 mg Tablet

A Preparation of COS Grade Rosuvastatin

The Ultimate choice in dyslipidemia

TABLE OF CONTENTS

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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.

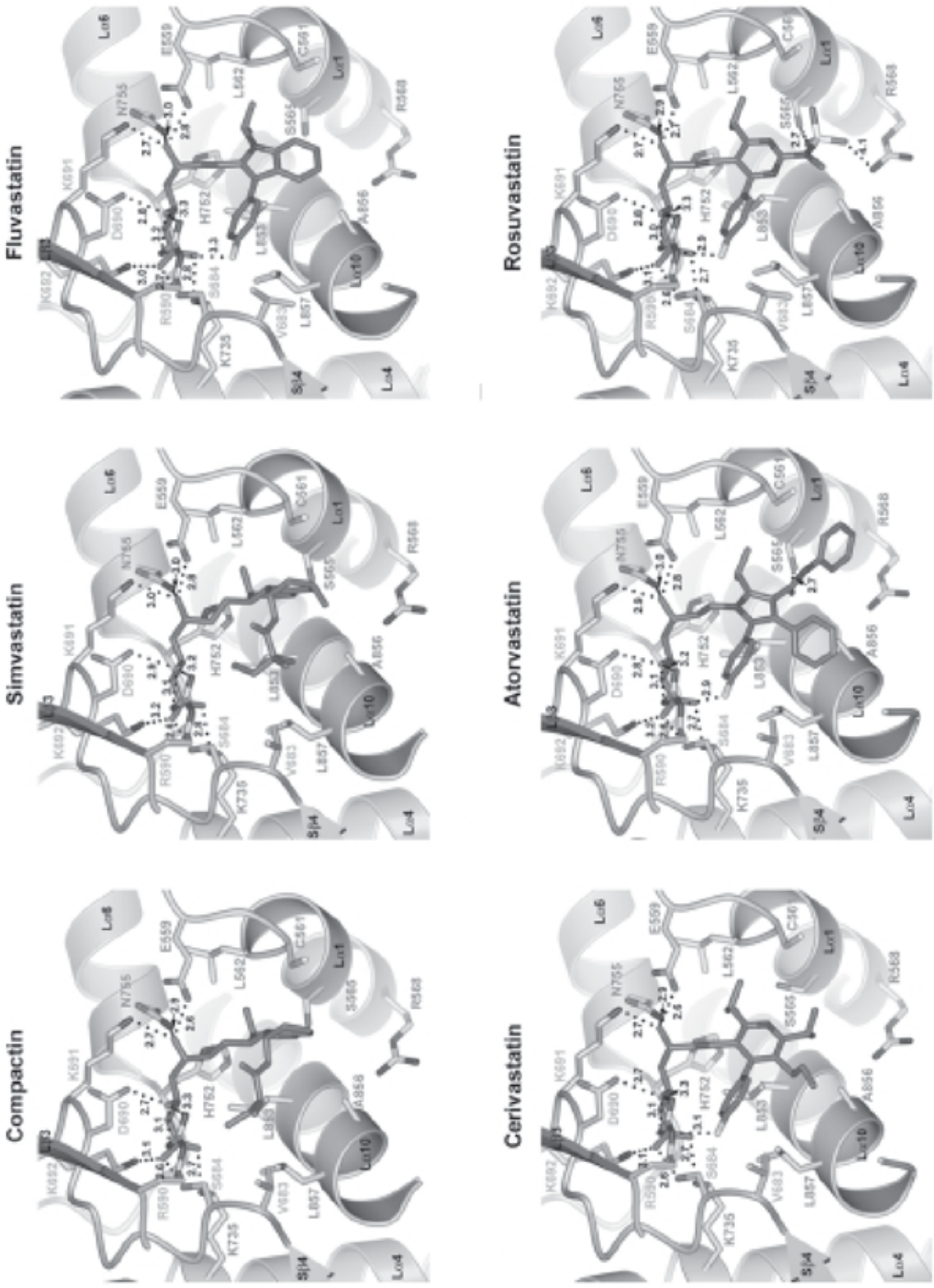

FIG. 1 Statin-HMG-CoA reductase complexes showing binding characteristics. Both rosuvastatin and atorvastatin form an additional hydrogen bond with the enzyme Ser^{565} residue, with binding occurring through the rosuvastatin sulfone oxygen atom or the atorvastatin carbonyl oxygen atom. In addition, 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).

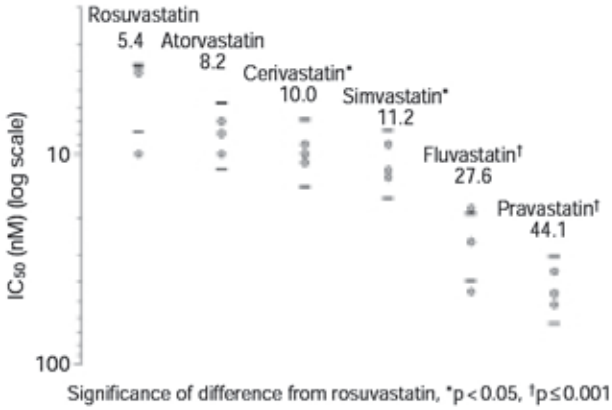

FIG. 2 Inhibition of purified human hydroxymethylglutaryl coenzyme A reductase catalytic domain by statins. Among the statins tested, rosuvastatin had the lowest 50% inhibitory concentration, followed by atorvastatin. Reproduced from Ref. No. 2 with permission.

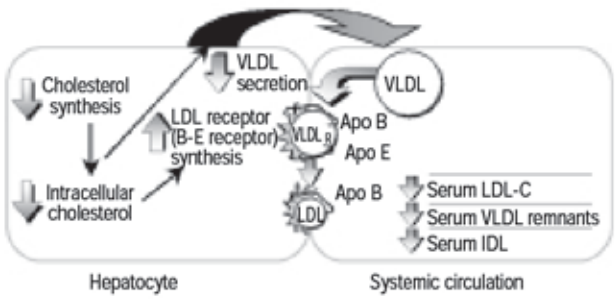

FIG. 3 Schematic representation of statin mechanism of action. Statins reduce hepatic cholesterol synthesis, lower levels of intracellular cholesterol, stimulate upregulation of the low-density lipoprotein (LDL) receptor, and increase uptake of non-high-density lipoprotein particles from the systemic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

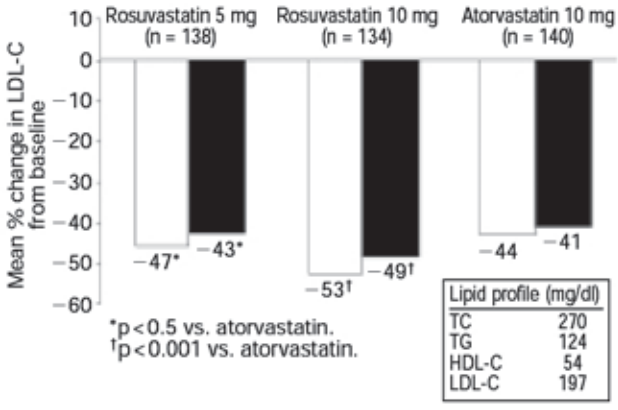

FIG. 4 Effects of rosuvastatin and atorvastatin at 52 weeks. In these hypercholesterolemic patients, starting doses of rosuvastatin 5 mg and 10 mg and atorvastatin 10 mg remained fixed for 12 weeks, after which doses could be titrated to achieve the Second National Cholesterol Education Project Adult 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

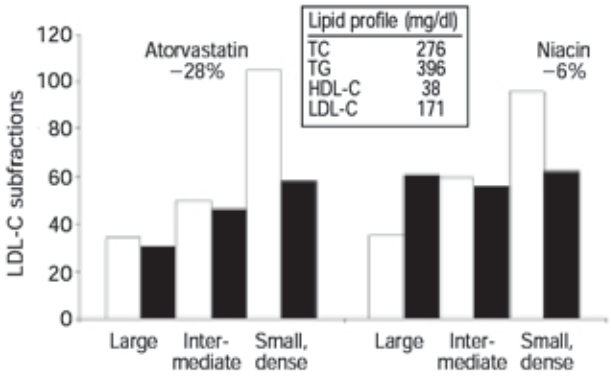

FIG. 5 Effect of atorvastatin 10 mg and niacin on low-density lipoprotein cholesterol (LDL-C) subfractions in patients with atherogenic dyslipidemia. Abbreviations as in Figure 4. □ = Baseline, ■ = treatment. Data are from Ref. No. 11.

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]

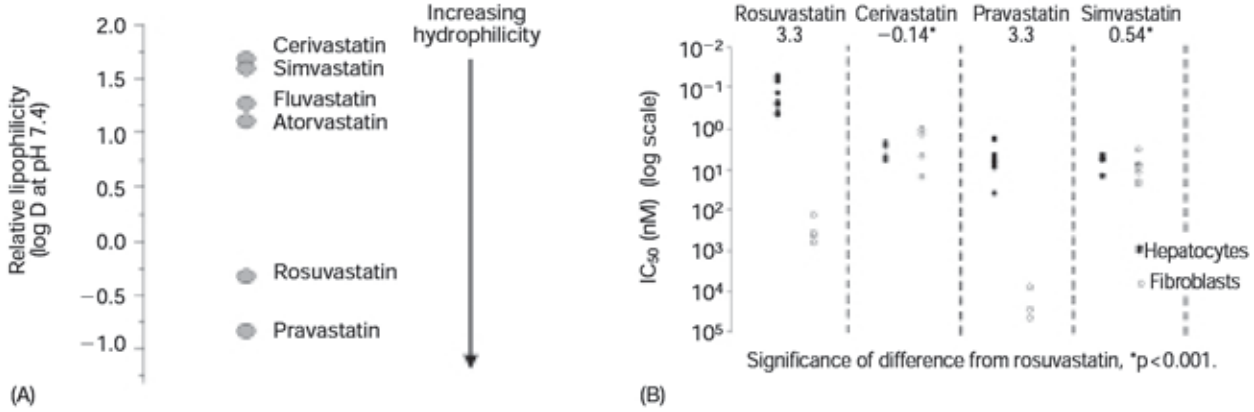

FIG. 6 (A) Relative lipophilicity/hydrophilicity of statins given as statin octanol-water coefficients (log D at pH 7.4).[2,16] (B) Log ratios of hydroxymethylglutaryl coenzyme A reductase inhibition for hepatocytes:fibroblasts among statins.[2,4] Adapted from Ref. No. 2.

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.

* For original article with references please visit: https://bit.ly/3t0oldw

ORIGINAL ARTICLE

A comparative evaluation of safety and efficacy of rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes mellitus with dyslipidemia

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AIM: To evaluate and compare the safety and efficacy of rosuvastatin, simvastatin, and atorvastatin in patients of type 2 diabetes mellitus with dyslipidemia. **MATERIALS AND METHODS:** This open-label, randomized, parallel group, comparative, prospective study of 12-weeks duration included 60 patients of type-2 diabetes with dyslipidemia having good glycemic control with fixed dose combination of tablet glimepiride + metformin and divided into three groups of twenty each. Group-1 patients have received tablet rosuvastatin 10 mg once daily, group-2 received tablet atorvastatin 10 mg once daily, and group-3 received tablet simvastatin 10 mg once daily for 12 weeks each. The levels of serum cholesterol, serum triglyceride, LDL, VLDL, and HDL were assessed at baseline and at the end of 12 weeks. **RESULTS:** The mean serum cholesterol, serum triglyceride, LDLc, and VLDLc levels were significantly reduced on therapy (P<0.001). Simultaneously, the mean levels of HDL were highly significantly increased (P<0.001) after therapy for 12 weeks with rosuvastatin, atorvastatin, and simvastatin. Reduction of LDL levels in rosuvastatin group was statistically significant when compared with those of simvastatin group (P< 0.05) but was statistically nonsignificant when compared with atorvastatin group (P> 0.05). Conclusion: 10 mg of rosuvastatin was comparable to 10 mg of atorvastatin and more efficacious than 10 mg simvastatin in reducing LDL levels after 12 weeks of therapy in patients of type 2 diabetes mellitus with dyslipidemia.

KEY WORDS: Aatorvastatin, dyslipidemia, rosuvastatin, simvastatin, type-2 diabetes mellitus

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Introduction

Diabetes mellitus is a very commonly occurring metabolic disorder characterized by hyperglycemia and altered metabolism of lipids, proteins, and carbohydrates which is due to absolute or relative deficiency of insulin or insulin resistance.[1]

Diabetes mellitus is associated with increased oxidative stress due to hyperglycemia. The oxidative damage plays a role in development of micro and macro vascular complications, leading to a significant impact on quality of life. Long-term complications involve almost all vital organs such as heart, eyes, kidney, blood vessels, and nervous system. These complications lead to the development of obesity, hypertension, dyslipidemia, and insulin resistance.[2]

There is a close association between complications of diabetes and diabetic dyslipidemia. Diabetic dyslipidemia accounts for around 80 percent diabetic deaths due to cardiovascular complications. There is a growing body of evidence to show that hyperglycemia and dyslipidemia are associated with excess of cardiovascular risk.[3]

Treatment of type 2 diabetes requires the agents that act beyond their blood glucose effect. Drug therapy that not only has an effect on blood glucose level but also has a beneficial effect on dyslipidemia, hypertension, obesity, hyperinsulinemia, and insulin resistance is likely to be the most useful therapy in treating type-2 diabetes.[4]

Diabetic patients tend to have a higher concentration of small dense LDL particles, which are associated with higher CHD risk. Lowering LDL levels is the first priority in treating diabetic dyslipidemia. Statins are the first

drug of choice, followed by resins or ezetimibe, then fenofibrate, or niacin. Current evidence and guidelines mandate that diabetic dyslipidemia should be treated aggressively, and lipid goals can be achieved in most patients with diabetes when all available products are considered and, if necessary, used in combination.[5]

Different statins require different dosing to reach the same LDL level. The lowering of LDL levels with statins varies from 20 to 60%. Therefore, the greatest effects are seen with the most potent statins such as simvastatin, atorvastatin, and rosuvastatin in the higher doses. Besides, majority of diabetic patients are at risk of coronary heart disease and deserve LDL cholesterol lowering to the currently recommended targets.[6]

The diabetes atorvastatin lipid intervention (DALI) study concluded that either 10 or 80 mg of atorvastatin is equally effective in the treatment of diabetic dyslipidemia.[7] Intensive lowering of LDL-C with high dose atorvastatin does not result in a significant reduction in the primary outcome of major coronary events, but reduces the risk of other composite secondary end points and nonfatal acute MI.[8]

Atorvastatin is more effective than simvastatin-based therapies in achieving treatment targets in patients with familial hypercholesterolemia.[9] Rosuvastatin 10 and 20 mg tablet improves the overall lipid profile of hypercholesterolemic patients better than does milligram equivalent doses of atorvastatin.[10]

Considering the above-mentioned facts, it seems that prevention of cardiovascular complications of diabetes must be considered as a national public health goal in the light of the increasing prevalence of the disease and the high frequency and seriousness of its complications.

The present study was thus planned to primarily evaluate and then to compare the efficacy and safety of newer emerging and promising statin rosuvastatin *vs* existing commonly used statins such as simvastatin and atorvastatin in patients with type-2 diabetes mellitus with dyslipidemia, so as to guide the present treatment strategies in the management of diabetes with dyslipidemia in Indian population.

Materials and Methods

This study was open-label, randomized, parallel group, comparative, prospective study in patients with type 2 diabetes mellitus with dyslipidemia. Sixty patients of type-2 diabetes with dyslipidemia having good glycemic control with fixed dose combination of tablet glimepiride + metformin were included in the study after taking written informed consent. The exclusion criteria for patients were clinically significant deviation from normal in physical examination, laboratory parameters, ECG, or chest X-ray. Clinically significant cardiovascular disease, including a history of congestive heart failure, angina pectoris within 1 year and history of myocardial infarction within 1 year, convulsive disorder, clinically significant gastrointestinal disease, including active peptic ulcers within the preceding 5 years, renal disease, hepatic disease, hematologic disease and insulin-dependent diabetes mellitus, and known infection with human immunodeficiency virus, were excluded. Subjects with the presence of any acute illness, h/o sensitivity to statins, history of any musculo-skeletal disorder, history of alcohol, barbiturate, marijuana, or multidrug abuse, participation in other investigational drug studies within 30 days before the start of the study, subjects who are unlikely to be compliant with the protocol requirements, pregnant or lactating females, patients with history of use of any of the statins for at least 6 months prior to the commencement of the study and smokers were also excluded.

Approval of the ethical committee of Government Medical College and Hospital, Aurangabad was taken prior to the start of the study. Sixty patients were enrolled in the study after satisfying the inclusion and exclusion criteria. Included patients were explained in detail about the study protocol and related hazards. Informed written consent was obtained from all the patients. Those included underwent all baseline investigations such as liver function tests, kidney function tests, blood sugar level, fundoscopy, and baseline lipid profile, which was repeated at the end of the study. Enrolled patients were divided into three groups of twenty each by computer generated randomization chart (calculated from True Epistat, Standard version 1999). Group-1 patients received rosuvastatin10 mg tablet once in a day, group-2 received atorvastatin tablet 10mg once in a day, and group-3 received simvastatin tablet 10 mg once daily for a period of 12 weeks. Each patient in the respective group was provided with the drug supplies for fifteen days and was asked to visit the diabetic clinic for follow up and for collection of drugs. At each follow-up visit, patients were assessed for glycemic control, and history pertaining to adverse drug effects was asked. All patients were given advice about diet and exercise.

The primary objectives for the study were:

1. To evaluate the effect of rosuvastatin, atorvastatin, and simvastatin on the lipid profile of patients with type 2 diabetes mellitus with dyslipidemia.
2. To evaluate the effect of atorvastatin on the lipid profile of patients with type 2 diabetes mellitus with dyslipidemia.

The secondary objective for the study was to compare the safety and efficacy of rosuvastatin with simvastatin and atorvastatin in patients with type 2 diabetes mellitus with dyslipidemia.

Results

Rosuvastatin, atorvastatin, and simvastatin were very effective in reducing the levels of serum cholesterol, serum triglyceride, LDL, and VLDL after treatment for 12 weeks in patients with type 2 diabetes mellitus with dyslipidemia. The reductions in these lipid parameters were highly significant. All the three statins also increased the levels of HDL significantly ($P < 0.001$) after treatment for 12 weeks [Table 1].

There was statistically significant increase in HDL (49.76 ± 5.04 *vs.* 45.48 ± 7.26, $P < 0.05$) levels in rosuvastatin group when compared with atorvastatin after therapy. However, the reductions in serum cholesterol, triglyceride, LDL, and VLDL showed no statistically significant difference in both the groups ($P > 0.05$) [Table 2].

When compared with simvastatin group, the patients of rosuvastatin group showed statistically significant reduction in serum cholesterol group (196.71 ± 32.57 *vs.* 217.01 ± 24.06, $P < 0.05$) and LDL levels (107.73 ± 32.87 *vs.* 134.49 ± 26.34, $P < 0.05$). The increase in HDL levels in rosuvastatin group was highly significant (49.76 ± 5.04 *vs.* 41.53 ± 7.06, $p < 0.001$) when compared with simvastatin group after treatment for 12 weeks. Serum triglycerides and VLDL showed no significant difference in both the groups ($P > 0.05$) [Table 3].

Atorvastatin significantly reduced LDL levels (114.27 ± 35.85 vs. 134.49 ± 26.34, P<0.05) as compared to simvastatin but showed no statistically significant difference (P > 0.05) in other studied lipid parameters of type 2 diabetics after treatment [Table 4].

Rosuvastatin reduced LDL levels by 44.25%, atorvastatin reduced LDL levels by 35.56%, and simvastatin reduced

Table 1: Comparative effect of rosuvastatin, atorvastatin and simvastatin on lipid profile parameter before and after therapy

Lipid profile parameter	Rosuvastatin Mean ± SD		Atorvastatin Mean ± SD		Simvastatin Mean ± SD	
(mgs %)	Before	After	Before	After	Before	After
Serum cholesterol	284.38 ± 50.81	196.71 ± 32.57	270.86 ± 43.32	201.11 ± 33.38	265.19 ± 29.41	217.01 ± 24.06
'P' value	< 0.001**	< 0.001**	< 0.001**			
Serum triglyceride	245.46 ± 32.42	196.06 ± 26.94	255.41 ± 45.13	221.84 ± 77.00	228.70 ± 29.37	205.90 ± 27.96
'P' value	< 0.001**	< 0.05 *	< 0.001**			
HDL	42.06 ± 3.30	49.76 ± 5.04	42.46 ± 7.71	45.48 ± 7.26	39.72 ± 6.87	41.53 ± 7.06
'P' value	< 0.001**	< 0.001**	< 0.001**			
LDL	193.23 ± 50.28	107.73 ± 32.87	177.34 ± 46.29	114.27 ± 35.85	179.73 ± 31.21	134.49 ± 26.34
'P' value	< 0.001**	< 0.001**	< 0.001**			
VLDL	49.09 ± 6.48	39.21 ± 5.39	51.05 ± 9.03	41.37 ± 8.24	45.74 ± 5.87	40.99 ± 5.71
'*P*' value	< 0.001**		< 0.001**		< 0.001**	

HDL: High-density lipoproteins, LDL: Low density lipoproteins, VLDL: Very low density lipoproteins, '*P*' <0.001 ** (Highly statistically significant), '*P* '< 0.05 * (Statistically significant)

Table 2: Comparative effect of rosuvastatin and atorvastatin on lipid profile parameter after therapy

Lipid profile parameter (mgs %)	After rosuvastatin therapy Mean ± SD	After atorvastatin therapy Mean ± SD	'*P*' value
Serum cholesterol	196.71 ± 32.57	201.11 ± 33.38	> 0.05
Serum triglyceride	196.06 ± 26.94	221.84 ± 77.00	> 0.05
HDL	49.76 ± 5.04	45.48 ± 7.26	< 0.05*
LDL	107.73 ± 32.87	114.27 ± 35.85	> 0.05
VLDL	39.21 ± 5.39	41.37 ± 8.24	> 0.05

HDL: High-density lipoproteins, '*P*' < 0.05 *(Statistically significant), LDL: Low density lipoproteins, VLDL: Very low density lipoproteins.

Table 3: Comparative effect of rosuvastatin and simvastatin on lipid profile parameter after therapy

Lipid profile parameter (mgs %)	After rosuvastatin therapy Mean ± SD	After simvastatin therapy Mean ± SD	'*P*' value
Serum cholesterol	196.71 ± 32.57	217.01 ± 24.06	< 0.05*
Serum triglyceride	196.06 ± 26.94	205.90 ± 27.96	> 0.05
HDL	49.76 ± 5.04	41.53 ± 7.06	< 0.001**
LDL	107.73 ± 32.87	134.49 ± 26.34	< 0.05*
VLDL	39.21 ± 5.39	40.99 ± 5.71	> 0.05

Table 4: Comparative effect of atorvastatin and simvastatin on lipid profile parameter after therapy

Lipid profile parameter (mgs %)	After atorvastatin therapy Mean ± SD	After simvastatin therapy Mean ± SD	'*P*' value
Serum cholesterol	201.11 ± 33.38	217.01 ± 24.06	> 0.05
Serum triglyceride	221.84 ± 77.00	205.90 ± 27.96	> 0.05
HDL	45.48 ± 7.26	41.53 ± 7.06	> 0.05
LDL	114.27 ± 35.85	134.49 ± 26.34	< 0.05*
VLDL	41.37 ± 8.24	40.99 ± 5.71	> 0.05

HDL: High-density lipoproteins, LDL: Low density lipoproteins, VLDL: Very low density lipoproteins, '*P*' <0.001** (Highly statistically significant), '*P*'< 0.05* (Statistically significant)

Table 5: Percentage changes on the various parameters of lipid profile after administration of rosuvastatin, atorvastatin, and simvastatin

Lipid profile parameter (mgs %)	Rosuvastatin group (%)	Atorvastatin group (%)	Simvastatin group (%)
Serum cholesterol	↓ 30.83	↓ 25.75	↓ 18.17
Serum triglyceride	↓ 20.13	↓ 13.14	↓ 9.97
HDL	↑ 18.31	↑ 7.11	↑ 4.56
LDL	↓ 44.25	↓ 35.56	↓ 25.17
VLDL	↓ 20.13	↓ 18.96	↓ 10.38

HDL: High-density lipoproteins, LDL: Low density lipoproteins, VLDL: Very low density lipoproteins

LDL levels by 25.17%. Rosuvastatin showed 30.83% reduction in cholesterol levels while atorvastatin and simvastatin reduced cholesterol levels by 25.75 and 18.17% respectively. The HDL levels were increased by 18.31, 7.11, and 4.56% in the rosuvastatin, atorvastatin, and simvastatin groups respectively [Table 5].

No adverse events were observed in any of the study groups. Rosuvastatin, atorvastatin, and simvastatin group did not deviate significantly from their baseline biochemical profile after 12 weeks of therapy.

Discussion

Type 2 diabetes is emerging as a major public health problem and seems to occur decade earlier in our country compared to the west. Diabetic care Asian-India study found 40% obesity in urban Indian type 2 diabetes mellitus. They also found inadequate glycemic control and late diabetic complications at the mean duration of one year in over 55 percent of patients.[11]

The evidence that lipid lowering drug treatment (especially statins) significantly reduces cardiovascular risk in diabetic and nondiabetic patients is strong and suggests that diabetic patients benefit more in both primary and secondary prevention.[12]

In the present study, the patients studied were type 2 diabetic patients with dyslipidemia, but having good glycemic control with fixed dose combination of tablet glimepiride + metformin. The criteria for evaluation were lipid profile parameters, namely, serum cholesterol, serum triglyceride, LDL, VLDL, and HDL.

Rosuvastatin decreased the levels of serum cholesterol, serum triglyceride, LDL, VLDL and increased the levels of HDL after therapy for 12 weeks. The difference in the studied lipid parameters after therapy was highly statistically significant ($P < 0.001$). These results are

in accordance with the pilot study with rosuvastatin conducted by Gleuck *et al,* at The Cholesterol Centre, Jewish Hospital, Cincinnati, USA.[13]

Atorvastatin and simvastatin also decreased the levels of serum cholesterol, serum triglyceride, LDL, VLDL and increased the levels of HDL after therapy for 12 weeks. The difference in the studied lipid parameters after therapy in both the drug groups was highly statistically significant ($P < 0.001$). These results are in accordance with the studies conducted by Goudevenos *et al*[14] and Lewin *et al,*[15] for the efficacy of atorvastatin and simvastatin in dyslipidemia, respectively.

When the LDL level reduction in rosuvastatin group with that of atorvastatin and simvastatin group was compared, it was observed that the reduction in LDL levels in rosuvastatin group were statistically significant when compared with those of simvastatin group, but were statistically nonsignificant when compared with atorvastatin group. These results are in contrast to a study conducted by Bullano *et al,* which concluded that rosuvastatin was more effective than both atorvastatin and simvastatin in reducing LDL levels significantly.[16]

The comparison of reduction in LDL levels between atorvastatin group and simvastatin group were statistically significant. This result is in accordance to a study conducted by Wu *et al,* which showed that patients treated with atorvastatin had a significantly greater reduction in low-density lipoprotein cholesterol as compared to simvastatin.[17]

The rise in HDL levels in rosuvastatin group after therapy was statistically significant when compared with atorvastatin group and was highly statistically significant when compared with simvastatin group. In contrast to this, the use of rosuvastatin *vs* atorvastatin in type 2 diabetes mellitus (URANUS) study group found that both rosuvastatin and atorvastatin increased HDL-C and decreased TG from baseline to 4 weeks, but there were no statistically significant differences between the groups.[18] The COMETS study (a comparative study with rosuvastatin in subjects with metabolic syndrome) concluded that rosuvastatin increased high-density lipoprotein cholesterol significantly more than atorvastatin.[19] However, the comparison of increase in HDL levels between atorvastatin group and simvastatin group were statistically nonsignificant. This result is in contrast to the study conducted by Hunninghake *et al,* which concluded that simvastatin produced larger increases in HDL-C.[20]

The comparison of the serum cholesterol reduction in rosuvastatin group with that of atorvastatin and simvastatin group revealed that the reduction in serum cholesterol levels in rosuvastatin group were statistically significant when compared with those of simvastatin group but were statistically nonsignificant when compared with atorvastatin group. The comparison of reduction in serum cholesterol levels between atorvastatin group and simvastatin group were statistically nonsignificant.

The intergroup comparison of reduction of serum triglycerides and VLDL after therapy among the rosuvastatin, atorvastatin, and simvastatin groups was statistically nonsignificant ($P > 0.05$).

Rosuvastatin reduced LDL levels by 44.25%, atorvastatin reduced LDL levels by 35.56%, and simvastatin reduced LDL levels by 25.17%. These results are consistent with the STELLAR trial where rosuvastatin, atorvastatin, and simvastatin reduced LDL levels by 45.8, 36.8, and 28.3%, respectively.[21]

Conclusion

In summary, 10 mg of rosuvastatin tablet was comparable to 10 mg of atorvastatin tablet and more efficacious than 10 mg tablet simvastatin in reducing LDL levels after 12 weeks of therapy in patients of type 2 diabetes mellitus with dyslipidemia. Also, 10 mg of rosuvastatin was more efficacious than 10 mg of both atorvastatin and simvastatin in increasing HDL levels after 12 weeks of therapy in patients of type 2 diabetes mellitus with dyslipidemia. No adverse events were noted with any of the three statins used. However, further studies are necessary to conclusively prove the efficacy of rosuvastatin over the existing statins.

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Clinical Medicine Insights: Cardiology

EXPERT REVIEW

Rosuvastatin: A Review of the Pharmacology and Clinical Effectiveness in Cardiovascular Disease

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Abstract: Rosuvastatin is a new generation HMG-CoA reductase inhibitor which exhibits some unique pharmacologic and pharmacokinetic properties. It has low extrahepatic tissue penetration, low potential for CYP3A4 interactions and substantial LDL-C lowering capacity and therefore has distinct advantages. We conducted a Medline literature search to identify rosuvastatin papers published in English. In this review, we outline the pharmacology of rosuvastatin, highlighting its efficacy and safety. We also review the major clinical trials with reference to primary and secondary prevention, familial hypercholesterolaemia and comparison with other statins. Finally we address its place in clinical practice.

Keywords: rosuvastatin, cardiovascular risk, statins, low density lipoprotein cholesterol

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Introduction

Ischaemic heart disease (IHD) is the leading cause of mortality worldwide and constitutes a major health burden. According to World Health Organisation (WHO) statistics it accounts for 12.8% of deaths, with stroke and other cerebrovascular disease accounting for a further 10.8%. In the United Kingdom, data from the Health Surveys for England suggest that while mortality may be declining, cardiovascular disease morbidity continues to rise. Epidemiological studies have established a strong correlation between cholesterol and the incidence of cardiovascular disease. The associated morbidity and mortality is positively correlated to low density lipoprotein cholesterol (LDL-C) and inversely related to high density lipoprotein cholesterol (HDL-C).[1,2]

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors that are effective in the reduction of total and LDL cholesterol.[3] A number of large randomized control trials have demonstrated unequivocally that lowering LDL-C particularly with statins reduces the risk of cardiovascular deaths and events.[4] HMG CoA inhibitors have been shown to prevent initial cardiovascular events and subsequent cardiovascular events in ischaemic heart disease patients, irrespective of the cholesterol concentration.[5,6] In addition to the beneficial cholesterol lowering effects, statins improve endothelial function, enhance stability of atherosclerotic plaques, and inhibit inflammatory as well as thrombogenic responses in arterial walls.[7] Furthermore extensive post marketing surveillance has shown that long term statin therapy is generally well tolerated.[8]

The lipid lowering arms of Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed the benefit of statin therapy in primary prevention of cardiovascular events.[9,10] The 4S study was the first study conclusively linking a statin with improved outcomes in patients with coronary heart disease. It established simvastatin as the most common LDL-C lowering treatment for patients with CHD in northern Europe.[11] Subsequently, more studies including results of the Treating to New targets (TNT) trial have shown that intensive lipid lowering (atorvastatin 80 mg) significantly reduces the risk of recurrent cardiovascular events compared to standard lipid lowering (atorvastatin 10 mg) in stable CHD patients.[12] Other clinical trials using various statins have confirmed similar beneficial effects for ameliorating cardiovascular risk in specific groups such as patients with diabetes, heart failure and renal failure. Early detection and treatment with statins has been shown to reduce morbidity and mortality in those with heterozygous familial hypercholesterolaemia.[13]

The reduction in cardiovascular events from statin therapy is proportional to the LDL-C reduction. A 1.0 mmol/L reduction in LDL-C results in a 20% decrease in major coronary events and revascularisation.[14] Larger reductions in LDL-C are associated with greater reductions in cardiovascular events, so more potent statins result in greater cardiovascular risk reduction. The drive towards more stringent goals for LDL-C lowering in cardiovascular risk prevention has brought high impact statin therapy into focus.[12] Different statins have varying effects on LDL-C reduction with rosuvastatin producing the greatest reduction and fluvastatin the least.[15] Statins vary in their lipophilicity and metabolism. These affect their extrahepatic tissue penetration and drug interactions with potential safety implications. Rosuvastatin which is a new generation HMG-CoA reductase inhibitor exhibits some unique pharmacologic and pharmacokinetics properties.[16] It has low extrahepatic tissue penetration, low potential for CYP3A4 interactions and substantial LDL-C lowering capacity and may therefore have some advantages. Its potential impact in primary and secondary prevention of cardiovascular disease in different groups including heart failure, elderly, renal failure and diabetes, and also in combination with other lipid lowering drugs is the subject of ongoing clinical studies.

In this review, we will outline the pharmacology of rosuvastatin; highlight its efficacy and safety. We will also review clinical studies with reference to primary and secondary prevention, familial hypercholesterolaemia and comparison with other statins. Finally we will address its place in clinical practice.

Pharmacology

Rosuvastatin is a fully synthetic HMG-CoA reductase inhibitor. Other HMG-CoA reductase inhibitors are either natural, mevinic acid derived (lovastatin, simvastatin, pravastatin) or synthetic, heptenoic acid derived (atorvastatin, fluvastatin). Rosuvastatin belongs to a

new generation of methane-sulphonamide pyrimidine and *N*-methane sulfonyl pyrrole-substituted 3, 5-dihydroxy-heptenoates. Although the characteristic statin pharmacophore remains similar to other statins, the addition of a stable polar methane-sulphonamide group provides low lipophilicity and enhanced ionic interaction with HMG-CoA reductase enzyme thus improving its binding affinity to this enzyme.[16–18]

Pharmacodynamics

Rosuvastatin competitively inhibits HMG-CoA reductase enzyme selectively and reversibly. This enzyme converts HMG-CoA to mevalonic acid in the cholesterol biosynthetic pathway which is the rate limiting step in cholesterol synthesis. Rosuvastatin therefore decreases hepatic sterol synthesis, which, in turn, leads to a decreased concentration of hepatocellular cholesterol. Hepatocytes respond to this decreased intracellular cholesterol concentration by increased synthesis of LDL receptors to enhance hepatic LDL reuptake from the circulation. The net result of this process is an increased fractional catabolism of LDL which reduces serum LDL-C concentration and total cholesterol.[19,20] Statins also reduce production of ApoB leading to reduced hepatic output of very low density lipoprotein cholesterol (VLDL-C) and triglycerides.[21] In patients with homozygous familial hypercholesterolaemia, rosuvastatin decreases LDL-C despite absence of functional LDL receptors. This may be secondary to marked inhibition of cholesterol synthesis which decreases LDL production. Rosuvastatin has demonstrated comparable reductions in triglyceride (TG) concentrations to other statins with the greatest benefit seen in patients with high baseline TG levels. Studies have shown rosuvastatin to increase HDL-C by 8%–12% with no clear relationship between the dose and response, although the increase is greatest in patients with low baseline HDL-C levels.[22,23] This may be due to reduction of cholesterol ester transfer protein (CETP).[24]

The affinity of rosuvastatin for the active site of the enzyme is four times greater than the affinity of HMG-CoA for the enzyme. It has the highest affinity for HMG-CoA reductase among statins marketed in Europe. This high affinity coupled with tight ionic interaction result in a slow recovery of enzyme activity after removal of rosuvastatin.[25] Since it is a hydrophilic statin, rosuvastatin relies on the organic anion transporting polypeptide-1B1 (OATP-1B1), which is strongly expressed on the hepatocyte basolateral membrane, as the key mechanism for active transport into hepatocytes. Its affinity for OATP-1B1 is comparable to atorvastatin but significantly greater than pravastatin or simvastatin. Rosuvastatin is therefore primarily distributed to hepatocytes while peripheral concentrations are low.[26]

As observed with other statins, rosuvastatin has pleiotropic effects independent of HMG-CoA reductase inhibition. These include improvements in endothelial function, anti-inflammatory, antithrombotic and anti-oxidant effects.[27] Rosuvastatin and other statins improve endothelial function by increasing the production of endothelial nitric oxide and reducing the production of oxygen derived free radicals. This in turn reduces endothelial dysfunction that has been implicated in atherosclerosis. Rosuvastatin reduces high sensitivity C reactive protein (hsCRP) which is a marker of inflammation and an independent cardiovascular risk predictor and other inflammatory markers.[28] Rosuvastatin inhibits platelet aggregation to leukocytes which inhibit formation of clots in injured endothelium.[29]

Pharmacokinetics

The oral bioavailability of rosuvastatin is 20%, which is comparable to atorvastatin, pravastatin and fluvastatin, and qualitatively higher than simvastatin and lovastatin. After a single oral dose the peak plasma concentration is reached at 5 hours. This is longer than other HMG-CoA inhibitors which achieve maximum plasma concentrations in less than 3 hours. In compiled data from pharmacokinetic trials, the peak plasma concentration and area under the concentration time curve show a largely linear relationship as the dose of rosuvastatin increases from 5 to 80 mg. Food intake decreases the rate of absorption of rosuvastatin by 20% but not the extent of absorption. This does not reduce the cholesterol lowering potency; therefore rosuvastatin can be taken with or without food, and in the morning or evening.[16,17,30]

Approximately 90% of rosuvastatin is protein bound mainly to albumin; other statins have approximately 95% protein binding except pravastatin which has a lower protein binding of 50%. The mean volume of distribution is 134 litres in steady state. Rosuvastatin is less lipophilic than other statins such

as atorvastatin and simvastatin but more lipophilic than pravastatin. Penetration of statins into extra-hepatic tissues occurs by passive diffusion and is dependent on their lipophilicity. This has implications on their muscle safety as increased rhabdomyolysis was reported in patients on lipophilic agents like cerivastatin and lovastatin.[31,32]

Human hepatocyte studies indicate that rosuvastatin is a poor substrate for metabolism by cytochrome P450 and hence 90% of the drug is excreted unchanged. CYP2C9 is the main isoenzyme involved in metabolism with minimal effect from CYP2C19.[33] Rosuvastatin is metabolised to an N-desmethyl metabolite which is less potent than the parent drug in inhibiting HMG-CoA reductase activity. The parent drug rosuvastatin is responsible for approximately 90% of plasma HMG-CoA inhibitor activity. Rosuvastatin is less likely to cause metabolic drug to drug interactions since it has limited metabolism by CYP isoenzymes. Other HMG-CoA reductase inhibitors such as atorvastatin and simvastatin are metabolised via CYP3A4. Their plasma concentrations are increased by inhibitors of CYP3A4 such as itraconazole, protease inhibitors and macrolide antibiotics.[16,30,33] Table 2 compares the pharmacokinetics of different statins.

Rosuvastatin has a plasma half life of 19 hours which is longer than atorvastatin (15 hours) and simvastatin (2–3 hours). It is primarily eliminated in the faeces (90%) compared with 10% renal excretion. Approximately 72% of absorbed rosuvastatin is eliminated in bile and 28% via renal excretion.[33]

Clinical Trials

There have been a number of clinical studies evaluating rosuvastatin on its own, against placebo and against other statins in various clinical settings.

Rosuvastatin in primary prevention

Clinical studies have demonstrated the benefits of statins in primary prevention. This is believed principally to be secondary to reduction in LDL-C, high sensitivity C-reactive protein (hsCRP) and elevation of HDL-C though other effects are recognised. The Cholesterol Treatment Trialists' Collaborators (CTT) meta-analysis established that a 1 mmol/L reduction in LDL cholesterol results in a 20% reduction in cardiovascular risk.[14] The benefit of statins in low risk populations was demonstrated in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study where reduction of cholesterol using pravastatin 10 mg reduced cardiovascular events by 33%.[35]

JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) marked an important juncture in primary cardiovascular disease prevention with statins. The participants had a mean Framingham risk score at baseline of 11.6% and would otherwise not have qualified for lipid lowering therapy. They were apparently healthy individuals with normal levels of LDL-C (<3.4 mmol/L) and increased hsCRP (>2 mg/L). The hsCRP threshold value of 2 mg/L is the approximate median hsCRP value after 30 days of statin therapy. It originated from secondary prevention trials and in particular the PROVE-IT-TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis In Myocardial Infarction) and A to Z (Aggrastat to Zocor) which showed that achieving this level of hsCRP was associated with improved cardiovascular outcomes.[36] JUPITER was a randomised, double blind, placebo-matched, multicentre trial conducted at 1315 sites in 26 countries. 17,802 participants received either 20 mg of rosuvastatin, or matched placebo, and were followed up every six months. 12 months into the study, the rosuvastatin group had a 50% lower median LDL-C, 37% lower median hsCRP and 17% lower median triglyceride level ($P < 0.001$ for all three comparisons) which persisted to study completion. The observed increase in HDL-C was transient. Results showed that rosuvastatin was associated with a significant reduction in first major cardiovascular events (HR 0.56; 95% CI, 0.46 to 0.69; $P < 0.00001$) which was the primary endpoint. Reductions were further seen in the incidence of the individual components of the trial end point including myocardial infarction (54%), stroke (48%), arterial revascularisation (47%), unstable angina and death from cardiovascular causes. This is important as up to 50% of all myocardial infarctions and strokes occur in patients with LDL cholesterol concentrations that are considered normal.[37] The benefits were largely similar for men and women, and were observed in all subgroups including age, ethnicity, region and cardiovascular risk score.

Table 1. Trial acronyms.

Acronym	Full meaning
AFCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
ANDROMEDA	A raNdomized, Double-blind, double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of Rosuvastatin (10 mg and 20 mg) and atOrvastatin (10 mg and 20 mg) in patiEnts with type 2 DiAbetes mellitus
ASTEROID	A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden
A to Z	Aggrastat to Zocor
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular Events
CARDS	Collaborative Atorvastatin Diabetes Study
CENTAURUS	Comparison of the Effects Noted in The ApoB:ApoA-I ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome
CORALL	Cholesterol Lowering Effects of Rosuvastatin compared with Atorvastatin in patients with type 2 diabetes
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
COSMOS	Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects
4D	Deutsche Dialyse Diabetes Study
GEOSTAT	Hepatic Metabolism and Transporter Gene Variants Enhance Response to Rosuvastatin in Patients With Acute Myocardial Infarction
GISSI-HF	Gruppo Italiano per lo Studio della Supravvivenza nell'Insufficienza cardiaca
IDEAL	Incremental Decrease in Endpoints through Aggressive Lipid Lowering
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LIPID	Long-term Intervention with Pravastatin in Ischaemic Disease
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
METEOR	Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin
MIRACL	Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering
ORION	Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation
PLUTO	Paediatric Lipid Reduction Trial of Rosuvastatin
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PULSAR	Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin
4S	Scandinavian Simvastatin Survival Study
SATURN	Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin
SHARP	Study of Heart and Renal Protection
SPACEROCKET	Secondary Prevention of Acute Coronary Events – Reduction of Cholesterol to Key European Targets Trial
STELLAR	Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses
TNT	Treating to New Targets
URANUS	Use of Rosuvastatin versus Atorvastatin in type 2 diabetes mellitus
WOSCOPS	West of Scotland Coronary Prevention Study

Previously, there has been limited data on statin benefits in women, black and Hispanic patients.

Since the results of JUPITER were initially published, several secondary subgroup analyses of the study population have been reported. Participants with a 10 year low baseline risk (<5%) benefited less than those with risk >5%. Participants with a 10 year intermediate baseline risk by Framingham (5%–20%) experienced incremental absolute risk reductions that were proportional to their global risk.[38] In a different subgroup analysis, participants at high global risk (10 year Framingham score >20%) showed no additional benefit for the combined endpoint of myocardial infarction, stroke and

Table 2. Pharmacokinetics of statins.

Comparative pharmacokinetics of statins							
Parameter	**Rosuvastatin**	**Atorvastatin**	**Simvastatin**	**Pravastatin**	**Fluvastatin**	**Pitavastatin**	**Lovastatin**
T_{max} (h)	3	2–3	1.3–2.4	0.9–1.6	0.4–2.1	0.6–0.8	2–4
Bioavailability	20	12	5	18	24	80	5
Lipophilicity	No	Yes	Yes	No	Yes	Yes	Yes
Protein binding	88	80–90	94–98	43–55	>98	96	95
Metabolism	Minimal CYP2C9 CYP2C19 Biliary excretion	CYP3A4	CYP3A4	Sulfation Biliary & urine excretion	CYP2C9	Minimal CYP2C8 CYP2C9	CYP3A4
Metabolites	Active (minor)	Active	Active	Inactive	Inactive	Active (minor)	Active
$T^1/_2$ (h)	19	15	2–3	1.3–2.8	1.2	10–11	2.9
Urinary excretion	10	2	13	20	6	NA	10
Faecal excretion	90	70	58	71	90	90	83

Note: Data from Soran et al.[34]
Abbreviations: T_{max}, time to peak plasma concentration; $T^1/_2$ (h), half life.

cardiovascular death (HR 0.50; 95% CI, 0.27 to 0.93) when compared with subjects who had an intermediate Framingham risk score.[39]

Another series of sub analyses have looked at lipid profiles and hsCRP particularly in relation to residual cardiovascular risk. In all of them, participants who achieved low concentrations of hsCRP in addition to low values of the lipid parameters of interest had the best outcome. When hsCRP is included in enrolment of primary prevention, rosuvastatin produced greater benefit when compared with other statins.[40]

These results compare favourably with other primary prevention trials using different statins. WOSCOPS (West of Scotland Coronary Prevention Study) showed that pravastatin 40 mg in men with moderate hypercholesterolaemia reduced incidence of myocardial infarction and cardiovascular death by 31%.[41] Similarly, AFCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) demonstrated that lovastatin 20–40 mg daily reduced risk of first major coronary event by 37% in men and women with average LDL-C and below average HDL-C when compared with placebo.[42] In the ASCOT lipid lowering arm, atorvastatin 10 mg reduced the incidence of myocardial infarction, stroke and cardiovascular death by 36% compared to placebo.[9] Figure 1 shows the CHD event reduction in primary prevention trials.

Rosuvastatin in secondary prevention

The beneficial effects of statin therapy in patients with ischaemic heart disease are well known. The 4S study showed that simvastatin 20 mg to 40 mg daily significantly reduced major coronary events, coronary death and overall mortality in patients post-MI or those with ischaemic heart disease.[43] In the LIPID study (Long-term Intervention with Pravastatin in Ischaemic Disease), pravastatin 40 mg reduced cardiovascular events and mortality in patients with history of myocardial infarction or unstable angina with different baseline lipid profiles.[44] Other studies

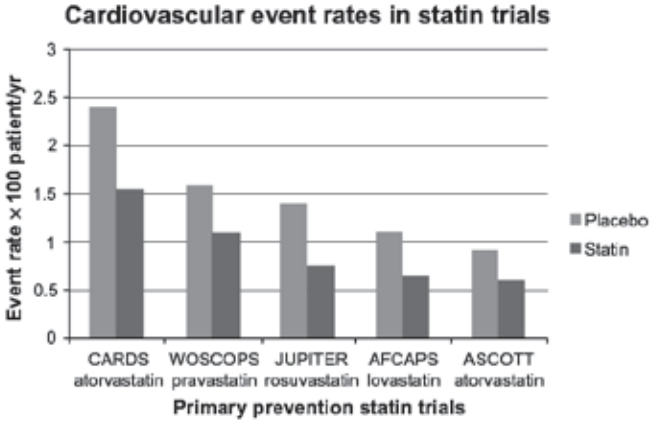

Figure 1. CHD event rate in primary prevention trials.

have also established the benefits of treatment after myocardial infarction.

a) Stable coronary heart disease (CHD)/Arrest and regression of atherosclerosis

The TNT trial comparing atorvastatin 80 mg with atorvastatin 10 mg, investigated whether intensive treatment to achieve LDL-C <1.81 mmol/L was associated with better outcomes. Mean LDL-C of 2 mmol/L was realised with intensive treatment. A relative risk reduction of 22% was achieved for the primary outcome which was the occurrence of a first major cardiovascular event.[12] The IDEAL study (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) compared the effect of atorvastatin 80 mg and simvastatin 20 mg on cardiovascular outcomes. There were significant reductions in non fatal acute myocardial infarction and in other secondary composite endpoints, with no difference in cardiovascular or all-cause mortality. Statistical significance was not demonstrated for the prespecified primary clinical outcome which was time to first occurrence of major coronary event.[45] In as much as there have been no clinical outcome data for secondary prevention with rosuvastatin, a number of studies have compared their effect on surrogate markers and achievement of treatment goals. The STELLAR study (Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses) showed that at different doses, rosuvastatin reduced total cholesterol better than other statins, and triglycerides better than simvastatin and pravastatin. Additionally a larger proportion of rosuvastatin patients achieved National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C targets when compared with atorvastatin.[46,47] PULSAR (Prospective Study to Evaluate Low Doses of Atorvastatin and Rosuvastatin) showed that in hypercholesterolaemic patients with vascular occlusive disease rosuvastatin 10 mg was better than atorvastatin 20 mg at reducing LDL-C, improving other lipid parameters and enabling achievement of US and European treatment goals.[47–49] Table 3 shows current LDL-C treatment targets.

Several studies have suggested that reduction in plaque volume is linked to the clinical outcome. ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived

Table 3. Current LDL-C treatment goals.

Guideline	Risk	Target
ESC	Very high risk	<1.8 mmol/L or 50% reduction if target unachievable
	High risk	<2.5 mmol/L
	Moderate risk	<3 mmol/L
JBS 2	High risk	2 mmol/L
NCEP ATP III	CHD	<100 mg/dL (2.6 mmol/L)
	≥2 risk factors	<130 mg/dL (3.4 mmol/L)
	0–1 risk factors	<160 mg/dL (4.2 mmol/L)

Abbreviations: ESC, European Society of Cardiology; JBS 2, Joint British Societies Guidelines on Prevention of Cardiovascular Disease in Clinical Practice; NCEP ATP III, National Cholesterol Education Programme Adult Treatment Panel III.

Coronary Atheroma Burden) investigated the impact of high dose rosuvastatin on regression of atherosclerosis. The results showed that rosuvastatin 40 mg produced significant reduction in LDL-C (53% from baseline; $P < 0.001$), increase in HDL-C (14.7% from baseline; $P < 0.001$) and regression of atheroma volume in the most diseased coronary arteries in 78% of participants. A median reduction of 6.8% in atheroma volume was recorded by IVUS (intravascular ultrasound). It must be noted that the study was non-comparative and open label.[50] Other studies including ORION (Outcome of Rosuvastatin Treatment on Carotid Artery Atheroma: a Magnetic Resonance Imaging Observation) and METEOR (Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin) demonstrated that rosuvastatin 40 mg achieved a 49% LDL-C reduction and slowed progression of atherosclerosis as assessed by carotid intima-media thickness (CIMT) but did not result in regression of CIMT. The lack of plaque regression may have occurred because low risk patients with minimal subclinical carotid atherosclerosis were used in the study. The COSMOS (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) study found that rosuvastatin achieved significant reduction of coronary plaque volume with good safety in stable Japanese CHD patients.[51,52] The recently concluded SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin)

study compared maximal doses of rosuvastatin and atorvastatin on coronary atheroma. It reported that although rosuvastatin achieved lower LDL-C and higher HDL-C, both agents produced similar percentage reduction in atheroma volume.[53]

b) Acute coronary syndrome (ACS)

The NCEP ATP III guidelines recommend that intensive statin treatment should be used in patients admitted with acute coronary syndrome.[47] The European Society of Cardiology (ESC) and the American College of Cardiology (ACC) have recommended LDL-C levels of 1.8 mmol/L as the optimal target for very high risk patients (established CHD, type I diabetes with end organ damage, moderate to severe chronic kidney disease (CKD) or a SCORE level >10%).[48] Several studies have provided evidence of the additional LDL-C lowering achieved by intensive statin therapy.

The PROVE-IT study found that intensive treatment with atorvastatin 80 mg was better than pravastatin 40 mg at preventing death and major cardiovascular events following ACS.[54] The A to Z study which compared 40 mg and 80 mg of simvastatin demonstrated a benefit which did not reach statistical significance, while the MIRACL (Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering) study showed that early intensive treatment with atorvastatin 80 mg after ACS led to a 16% reduction in death, acute MI, unstable angina and cardiac arrest, compared with placebo.[55] Meta-analyses of intensive statin trials have also shown that intensive treatment provides benefit above lower intensity treatment in prevention of myocardial infarction and strokes in patients with known coronary disease irrespective of the baseline LDL-C. The CENTAURUS (Comparison of the Effects Noted in The ApoB:ApoA-1 ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome) study showed that 20 mg rosuvastatin produced similar changes in ApoB:ApoA-1 ratio at 3 months when compared with atorvastatin 80 mg. Previous studies have identified ApoB:ApoA-1 ratio as an important predictor of myocardial infarction. In the same study rosuvastatin 20 mg achieved similar LDL-C reduction as atorvastatin 80 mg. This study therefore showed that rosuvastatin 20 mg is as effective as atorvastatin 80 mg in intensive statin therapy.[56] In SPACEROCKET (Secondary Prevention of Acute Coronary Events—Reduction of Cholesterol to Key European Targets Trial), a larger proportion of patients on rosuvastatin 10 mg achieved ESC, ACC and American Heart Association (AHA) optimal LDL-C target of less than 1.81 mmol/L when compared to those on simvastatin 40 mg. A crucial observation of this study was that in both treatment arms, most patients did not achieve these targets, highlighting the importance of intensive statin therapy to meet these goals. The superior lipid lowering effect of rosuvastatin makes it a good candidate for intensive lipid lowering.[57]

Rosuvastatin in women

Previous primary prevention trials have poorly demonstrated reduction in coronary events in women. In JUPITER the relative risk reduction in the primary end point and overall mortality was similar in men and women. Although women benefited more than men with regard to revascularisation/unstable angina, no significant benefit was seen for myocardial infarction, stroke or death from cardiovascular causes.[58]

Rosuvastatin in the elderly

Randomised control trial (RCT) data are limited regarding statin efficacy in the elderly. 5695 participants from JUPITER were >70 years at recruitment. They accounted for 49% of the confirmed primary end points in the trial. Analysis of this group showed an absolute risk reduction of the primary end point 48% greater than that observed in younger subjects. There were no serious safety concerns raised for this age group compared with younger subjects.[59]

Rosuvastatin in renal disease

Advanced kidney disease is associated with high cardiovascular morbidity and death. RCT evidence has shown an inconsistent relationship between cardiovascular outcome and LDL-C in haemodialysis patients. WOSCOPS showed benefit only in mild stages of CKD (eGFR > 60 mL/min per 1.73 m^2). In JUPITER, participants with moderate CKD benefited as much as those with preserved renal function in terms of primary end point reduction and faired better for all-cause mortality.[60]

AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Haemodialysis: An Assessment of Survival and Cardiovascular

Events) investigated the effects of rosuvastatin on cardiovascular risk in haemodialysis patients. It was a randomised, double blind, placebo-matched, multicentre trial involving 2776 patients aged 60–80 years. Good median reductions were achieved in LDL-C (42.9%), total cholesterol (26.6%), triglycerides (16.2%) and hsCRP (11.5%). Despite these reductions, there was no significant effect of treatment on the composite primary end point (time to a major cardiovascular event) or its individual components (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). This lack of efficacy was seen in all prespecified subgroups including diabetes, known CHD, hypertension, elevated hsCRP and high HDL-C. Thus, no relationship was demonstrated between cardiovascular end points and either baseline or follow up LDL-C. A further evaluation of secondary outcomes showed no reduction in all-cause mortality or non-cardiovascular death.[61] Similar results have been obtained from the 4D study which looked at atorvastatin.[62] In contrast to these studies, the SHARP (Study of Heart and Renal Protection) study which compared a combination of simvastatin 20 mg and ezetimibe 10 mg to placebo, found 17% reduction in major atherosclerotic events per 0.85 mmol/L reduction in LDL-C in CKD patients.[63] The implication of these findings is that some of the cardiovascular morbidity and mortality in haemodialysis patients may not be mediated by atherogenic processes.

Rosuvastatin in diabetes

Type 2 diabetes is associated with increased risk of coronary heart disease. In the UK Prospective Diabetes Study (UKPDS), every 1 mmol/L increment in LDL-C was associated with a 57% increase in relative risk of coronary heart disease. Furthermore, the LDL-C of diabetic patients predicted their risk of stroke.[64] CARDS (Collaborative Atorvastatin Diabetes Study) showed that atorvastatin 10 mg led to a reduction in cardiovascular events and strokes in diabetes patients without high HDL-C and no prior history of cardiovascular disease.[65] This has strengthened the need for statin therapy for primary prevention in diabetes patients. Sub-group analyses of 4S showed the benefits of simvastatin in reducing major coronary events and revascularisation in diabetic patients with coronary heart disease. However, the reduction in total and cardiovascular mortality was not significant due to the small sample size.[66]

A randomised double blind double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of rosuvastatin (10 mg and 20 mg), and atorvastatin (10 mg and 20 mg) in patients with type 2 diabetes mellitus (ANDROMEDA) showed that rosuvastatin produced greater reductions in LDL-C, ApoB and total cholesterol when compared with equal doses of atorvastatin. A greater proportion of patients on rosuvastatin achieved European LDL-C goals compared to those on atorvastatin.[67] The CORALL (Cholesterol Lowering Effects of Rosuvastatin compared with Atorvastatin in patients with type 2 diabetes) study showed that rosuvastatin produced greater reductions in ApoB:ApoA-1 ratios, LDL-C and total cholesterol in diabetic patients with moderate dyslipidaemia.[68] The superior effect of rosuvastatin compared with atorvastatin in reduction of LDL-C was also demonstrated in the URANUS (Use of Rosuvastatin versus Atorvastatin in type 2 diabetes mellitus) study.[69]

Familial hypercholesterolaemia (FH)

Many FH guidelines recommend a >50% reduction of LDL-C in heterozygous FH. Studies comparing different lipid lowering regimens demonstrate that only high impact therapy with rosuvastatin 40 mg or atorvastatin 80 mg achieves this goal when administered as monotherapy.[70] In all other circumstances, combination therapy with ezetimibe, bile acid sequestrants, fibrates, nicotinic acid or fish oils is often required.[71] There are no randomised control trial (RCT) outcome data with these combinations in FH. Whereas it is accepted that LDL apheresis and plasmapheresis are suitable treatments for homozygous FH, there are no RCTs comparing LDL apheresis and drug treatment alone. The use of LDL apheresis in heterozygous FH patients is thus unclear and at present maximal drug therapy is the preferred treatment.

Rosuvastatin in heart failure

The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) investigated the effect of rosuvastatin 10 mg in patients with New York Heart Association functional class II-IV systolic heart failure from ischaemic heart disease. The CORONA study did not establish any reduction in composite

cardiovascular outcome and death despite favourable effects on LDL-C, triglycerides, HDL-C and CRP. The use of rosuvastatin did however reduce hospitalisation from cardiovascular causes.[72] A similar trend was found in the GISSI-HF study in which only 40% of patients had ischaemic heart failure. In the GISSI HF (Gruppo Italiano per lo Studio della Supravvivenza nell'Insufficienza cardiac) study, rosuvastatin 10 mg had no effects on primary and secondary endpoints when compared with placebo.[73] The two studies show that rosuvastatin did not have extra benefit in reduction of cardiovascular mortality in patients with ischaemic and non-ischaemic heart failure.

Rosuvastatin in children

Studies in children with heterozygous FH have shown the safety and efficacy of statins, including their effect on carotid intima thickness and arterial flow mediated dilation.[74] PLUTO (Paediatric Lipid Reduction Trial of Rosuvastatin) investigated the efficacy and safety of incremental doses of rosuvastatin in achieving LDL-C treatment targets of <110 md/dL (2.87 mmol/L). A daily dose of rosuvastatin 5, 10 and 20 mg lowered LDL-C by 38, 45 and 50% respectively, with 40% of participants achieving the target. 68% of participants achieved the less stringent goal of LDL-C <130 mg/dL (3.4 mmol/L). This is far better than the adult FH population in who only 22% and 37% will achieve this LDL-C on 20 and 40 mg of rosuvastatin respectively. The effects on other lipid parameters and safety were consistent with other statin studies in adults and children.[75]

Stroke

JUPITER showed a 51% reduction in ischaemic stroke with rosuvastatin, though no beneficial effects were observed for transient ischaemic attacks or haemorrhagic strokes. These benefits were present in all patient groups including women, non smokers and other low risk patients. There was a 39% relative risk reduction of stroke per 1 mmol/L reduction in LDL-C. The beneficial effects were most marked for those who achieved LDL-C <1.8 mmol/L and hsCRP <2 mg/L.[40] Previous studies with other statins such as WOSCOPS and MEGA did not show significant reduction in stroke.[41,35] Rosuvastatin not only reduces the risk of stroke as shown in JUPITER but also slows the rate of progression of carotid atherosclerosis as observed in the ORION and METEOR studies.[51] There has not been any study investigating the effect of rosuvastatin in the secondary prevention of strokes in patients with previous history of stroke. The SPARCL study showed that intensive statin therapy with atorvastatin 80 mg daily resulted in significant reduction in recurrent stroke.[76] A secondary analysis of the SPARCL study found that the effect was greater in patients with established carotid stenosis at baseline. Intensive therapy with rosuvastatin may yield similar benefits.

Highly Active Antiretroviral Therapy (HAART)

HIV patients on highly active antiretroviral therapy are increasingly found to have hypercholesterolaemia and hypertriglyceridaemia. Prospective studies have also shown that these patients have increased incidence of cardiovascular events.[77] Current guidelines recommend statins to treat dyslipidaemia in HIV patients on HAART. Since 90% of rosuvastatin is excreted unchanged in bile with only 10% metabolised by CYP2C9 and CYP2C19, rosuvastatin has minimal drug–drug interactions with most antiretroviral drugs metabolised by CYP3A4.[78]

Protease inhibitors such as ritonavir, saquinavir and atazanavir inhibit OATP-1B1 the transporter protein involved in the hepatic cell uptake of rosuvastatin. This leads to higher serum rosuvastatin concentrations in patients taking protease inhibitors. It is recommended that lower doses of rosuvastatin are used in patients taking protease inhibitors. There are no known drug interactions between rosuvastatin and non nucleoside reverse transcriptase inhibitors (NNRTIs).[79]

A large retrospective cohort study in America found that rosuvastatin produced the largest reduction in LDL-C, non-HDL-C and triglycerides when compared with atorvastatin and pravastatin. It also produced the highest proportion of patients achieving target LDL and non-HDL-C without a difference in toxicity profile when compared with atorvastatin and pravastatin.[80] The British HIV association recommend the use of rosuvastatin in patients receiving HAART.[77]

Safety

In the pooled safety data of controlled Phase II/II trials, the incidence of adverse events during rosuvastatin therapy was comparable to those of other statins.

Subsequent meta-analysis of clinical trials and post marketing experience have consistently shown that rosuvastatin has a comparable safety profile to other available statins when used at 10 mg to 40 mg daily dose.[8] In JUPITER, hepatic injury, myopathy and cancer did not occur more frequently with rosuvastatin than with placebo, despite the fact that LDL-C < 55 mg/dL (1.4 mmol/L) were achieved in half of the rosuvastatin group.[40] AURORA reported a high incidence of adverse and serious adverse events which is consistent with previous studies in haemodialysis patients.[61]

A recent large prospective cohort study of primary care patients from 368 general practices in England and Wales reported findings from 225,922 patients who commenced statin therapy between 2002 and 2008. There were no clinically significant associations between any statins and Parkinson's disease, rheumatoid arthritis, venous thromboembolism, dementia, osteoporotic fracture, gastric cancer, lung cancer, melanoma, renal cancer, breast cancer and prostate cancer. The study further showed that with the exception of fluvastatin, all statins were associated with a dose dependent increased risk of myopathy. A direct comparison test between the individual statins did not yield a significant difference in men ($P = 0.57$) or women ($P = 0.61$). All statins were associated with a dose dependent increased risk of liver dysfunction. The highest risk was associated with fluvastatin while pravastatin and rosuvastatin had the lowest risks. Table 4 shows the hazard ratios of developing myopathy or liver dysfunction with different statins.

Rosuvastatin at every prescribed dose compared favourably with other statins with regard to liver dysfunction, myopathy, cataract, oesophageal cancer and acute renal failure.[81] A meta-analysis of randomised controlled trials on statins showed that there was a positive association between statins and the incidence of diabetes. The combined data reported a 0.39% absolute risk of developing diabetes with 4 years of statin therapy. The risk was higher in older participants of the statin trials. The absolute risk of developing diabetes was 0.6% with rosuvastatin (JUPITER, CORONA), 0.4% with atorvastatin (ASCOT-LLA) and 0.3% for simvastatin (4S). Paradoxically, there was a reduced incidence of diabetes with pravastatin (WOSCOPS, LIPID). It therefore appears that the risk of developing diabetes is marginally higher with rosuvastatin compared to other statins.[82] Other studies that involved rosuvastatin such as JUPITER, CORONA and GISSI HF all had an increased incidence of diabetes in the patients receiving rosuvastatin compared to placebo.[40,72,73] The overwhelming benefit of statins in the reduction of cardiovascular events outweighs the small risk of developing diabetes therefore statin therapy should be used in patients with high cardiovascular risk. All statins can cause myopathy and rhabdomyolysis especially at higher doses. Combination of statins with other medications may lead to increased risk if these medication increase plasma concentrations of the statins. Cases of rhabdomyolysis have been report in patients on medications which increase plasma concentrations of rosuvastatin such as gemfibrozil, liponavir and ritonavir. Table 5 shows drugs which can interact with rosuvastatin.

One unique effect of rosuvastatin is the dose dependent transient proximal isolated low-molecular-weight

Table 4. Adverse outcomes of statins.

Adverse outcomes	Statin	Hazard ratio ♀ (95% CI)	Hazard ratio ♂ (95% CI)
Moderate/severe myopathy	None	1.00	1.00
	Simvastatin	3.30 (2.32–4.69)	6.11 (4.79–7.80)
	Atorvastatin	2.62 (1.42–4.84)	8.18 (5.82–11.50)
	Fluvastatin	Insufficient data	1.20 (0.17–8.53)
	Pravastatin	2.68 (0.99–7.25)	5.79 (3.07–10.91)
	Rosuvastatin	5.41 (2.64–11.07)	4.19 (1.86–9.45)
Moderate/severe liver dysfunction	None	1.00	1.00
	Simvastatin	1.62 (1.41–1.86)	1.79 (160–2.01)
	Atorvastatin	2.00 (1.64–2.44)	1.86 (1.55–2.24)
	Fluvastatin	3.08 (2.14–4.43)	2.37 (1.66–3.38)
	Pravastatin	1.91 (1.37–2.65)	1.13 (0.78–1.62)
	Rosuvastatin	1.31 (0.87–1.97)	1.46 (1.01–2.11)

Data from Hippisley-Cox et al.[81]

Table 5. Rosuvastatin drug interactions.

Drugs that increase plasma concentrations of rosuvastatin
Drugs that antagonise organic anion transporting polypeptide 1B1
Gemfibrozil
Protease inhibitors: ritonavir, liponavir
Cyclosporin
Drugs that reduce plasma concentrations of rosuvastatin
Antacids
Erythromycin
Drugs affected by co-administration with rosuvastatin
Warfarin increased INR
Ethinyl oestradiol: increased concentrations

proteinuria which appears to have no effect on glomerular function.

Efficacy

The STELLAR study showed the greater efficacy of rosuvastatin in improving LDL-C, triglycerides and HDL-C. It is the most effective statin at increasing HDL-C and has a positive effect on apolipoprotein and lipid ratios. Most of the lipid modifying benefit observed in the study was achieved at a 10 mg daily dose.[46] PULSAR compared the efficacy and safety of rosuvastatin 10 mg with atorvastatin 20 mg in high risk patients with vascular occlusive disease. Rosuvastatin 10 mg was better than atorvastatin 20 mg at improving LDL-C, HDL-C, triglycerides and ApoB/ApoA-1 ratio. It also enabled a greater proportion of treated patients to NCEP ATP III and ESC goals.[49] Table 6 compares the efficacy of different statins.

Intermittent rosuvastatin

Several small studies have reported that alternate-day therapy with rosuvastatin has important benefits in addition to improving the lipid profile. These include limitation of adverse reactions, enhanced patient compliance and reduced cost of treatment.[83] Other studies have looked at weekly rosuvastatin for patients with previous statin intolerance. One study achieved reductions of 23% in LDL-C, 17% in total cholesterol, 12% in triglycerides and an increase of 5% in HDL-C in patients who had a prior history of adverse reactions to one or more statins.[84] These alternative dosing regimens have not been proven to reduce cardiovascular risk. A few studies have started reporting the effects of pulsed combination drug therapy involving rosuvastatin in their regimens.[85]

Combination therapy

Very high risk patients or those with severe dyslipidaemia often require combination therapy to achieve treatment goals and enhance lipid profile modification. In one study combination of rosuvastatin 5 mg to 20 mg with fenofibric acid demonstrated significant efficacy in lowering triglycerides and increasing HDL-C when compared with rosuvastatin alone. Furthermore the combination of rosuvastatin with fenofibric acid was well tolerated and as safe as each drug used as monotherapy.[86] Similar results were found by Durrington when combination of rosuvastatin and fenofibrate was used in type 2 diabetes.[87] Further clinical trials are required to establish the benefits in clinical outcomes of combination of rosuvastatin with fenofibrate. The use of rosuvastatin 40 mg with fenofibric acid or fenofibrate has not been evaluated and should therefore not be prescribed routinely.[88] Several studies have shown the efficacy and safety of rosuvastatin in combination with ezetimibe, bile acid sequestrants and fish oils.[89,90] Some small trials and angiographic studies have demonstrated some benefit

Table 6. Efficacy of statins.

Comparative efficacy of statins						
% LDL-C reduction	**Rosuvastatin**	**Atorvastatin**	**Simvastatin**	**Pravastatin**	**Fluvastatin**	**Lovastatin**
<25	5	10	5	10–20	20	10–20
25–35	5	10	10–20	20–40	40–80	20–40
35–45	5–10	10–20	20–40	80		80
45–55	10–20	20–40	80			
55–60	20–40	80				
60–65	40–80					

Data from White.[16]

from combination therapy though this has not been corroborated by randomised clinical trial data.

Cost effectiveness

Economic evaluations show that intensive lipid lowering is a cost effective treatment for very high risk patients groups including those with ACS, heterozygous FH and diabetes. For these purposes, rosuvastatin 40 mg daily was the most optimal treatment based on 2009 prices for statins, providing generic atorvastatin 80 mg was not available.[91] A similar observation was made for lower treatment doses in the PULSAR trial. At the time of the study (2006), annual acquisition costs were lower for rosuvastatin 10 mg than atorvastatin 20 mg in the UK and the US.[49] Our group demonstrated in the GEOSTAT (Hepatic Metabolism and Transporter Gene Variants Enhance Response to Rosuvastatin in Patients With Acute Myocardial Infarction) study that patients with CYP3A5 and/or BCRP variant genotypes who were treated with rosuvastatin achieved treatment targets more frequently than those on simvastatin 40 mg. These results indicate the potential value of genetic profiling of patients to optimise statin response in a cost effective manner.[92]

Place in Therapy

Rosuvastatin is a potent statin with pharmacologic and pharmacokinetic advantages. Its high affinity for OATP-1B1 ensure a high hepatocyte concentration which results in superior efficacy at lowering LDL-C and TG as well as improving HDL-C and ApoB:ApoA-1 ratio compared to other statins. A possible exception is pitavastatin. Rosuvastatin is synthetic with a relatively low lipophilicity when compared with other statins and has minimal entry into peripheral cells. This, coupled with its minimal CYP450 metabolism confers relatively better tolerability, safety and drug interaction profile. As the circulating half life is 19 hrs it can be taken once daily at any time of the day regardless of meals.

Clinical trial data and post marketing surveillance have demonstrated important information about rosuvastatin. Several cardiovascular outcome studies have confirmed the beneficial effects that had been anticipated from vascular imaging studies. JUPITER showed the reduction in cardiovascular events and all cause mortality of rosuvastatin in primary prevention in patients with lower cardiovascular risk. This is the only statin that has been shown to reduce cardiovascular and all cause mortality.[40] Some authors believe that some of the benefits may have been exaggerated by the short duration of the study. Comparative studies have shown the potential benefits of rosuvastatin in secondary prevention and high intensity therapy.[46,49] The long term and legacy effects of rosuvastatin on cardiovascular mortality are awaited. A small increase in diabetes among those >65 years has been observed in rosuvastatin trials, but this occurs with other statins with the exception of pravastatin.[78] Physicians should be aware of the risk of proteinuria in patients on rosuvastatin and should screen for this. Given its potency and safety, rosuvastatin is a versatile statin that can be used in different clinical contexts.

Patients with a 10 year cardiovascular risk of >20% require intensive treatment to achieve LDL-C <2 mmol/L or a >50% reduction from baseline. These include patients with established CHD, moderate to severe CKD, type 1 and type 2 diabetes. Only rosuvastatin 20 mg–40 mg and atorvastatin 80 mg achieve this reduction as monotherapy. A large proportion of these patients are on multiple drug therapy and thus it is crucial to limit pill burden and avoid drug interactions. Most lipid therapy is now aimed at achieving treatment goals from guideline bodies such as ESC, JBS and NCEP ATP III. A new category of patients is thus created by those who fail to achieve these goals with various treatments. Such patients should be considered for treatment with rosuvastatin.

Special groups

Patients with hereditary hyperlipidaemia, particularly FH and FCH should be considered for early treatment with rosuvastatin. Their baseline LDL-C is invariably too high for less potent statins to reduce adequately. Furthermore these patients are at extremely high cardiovascular risk. Patients on HAART should be considered for treatment with rosuvastatin whenever their treatment allows. In this patient group, choice is often limited and determined by the anti-retroviral regimen. They are also at very high cardiovascular risk. Certain patient groups such as those with renal failure and the elderly are at increased risk of statin related myopathy and rhabdomyolysis. Because of its potency, rosuvastatin can be used at very low doses. A number of reports are emerging about intermittent or pulsed therapy which is better tolerated yet

maintains reasonable lipid control. As with other potent statins, lower doses of rosuvastatin should be used in patients from South East Asia to reduce risk of rhabdomyolysis.

In conclusion rosuvastatin is an effective and safe statin which is ideal second line treatment for most patients requiring primary or secondary prevention. When there is a history of previous statin intolerance or multiple drug therapy, low dose rosuvastatin may be considered. For patient groups at very high risk where stringent LDL-C reduction is envisaged, rosuvastatin should be considered as a potential first line treatment. Its benefits against cost in patients with lower cardiovascular risk remain an issue of debate.

Abbreviations

ACC, American College of Cardiology; ACS, Acute coronary syndrome; AHA, American Heart Association; Apo A-1, Apolipoprotein A-1; ApoB, Apolipoprotein B; BCRP, Breast cancer resistance protein; CHD, Coronary heart disease; CYP3A4, Cytochrome P450 3A4; CETP, Cholesterol ester transfer protein; CYP2C9, Cytochrome P450 2C9; CYP2C19, Cytochrome P450 2C19; CIMT, Carotid intima media thickness; CKD, Chronic kidney disease; CRP, C-reactive protein; CYP3A5, Cytochrome P450 3A5; CYP450, Cytochrome P450 mixed function oxidase system; ESC, European Society of Cardiology; FCH, Familial combined hypercholesterolaemia; FH, Familial hypercholesterolaemia; HAART, Highly active antiretroviral therapy; HDL-C, High density lipoprotein cholesterol; HIV, Human immunodeficiency virus; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; hsCRP, High sensitivity C-reactive protein; IVUS, Intravascular ultrasound; JBS, Joint British Societies; LDL-C, Low density lipoprotein cholesterol; NCEP ATP III, National Cholesterol Education Programme Adult Treatment Panel III; NNRTI, Non nucleoside reverse transcriptase inhibitors; OATP-1B1, Organic anion transporting polypeptide 1B1; RCT, Randomised control trial; TG, Triglycerides; VLDL-C, Very low density lipoprotein cholesterol; WHO, World Health Organisation.

Declaration of Interest

JHB and ASH were investigator and principal investigator for the SPACEROCKET study which was funded by an unrestricted educational grant and both have received honoraria for speaking at AstraZeneca sponsored meetings. ASH has received fees consulting for AstraZeneca. No fee has been received for preparation of the manuscript.

Disclosures

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Review Article

Safety of statins

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ABSTRACT

Statins are an established class of drugs with proven efficacy in cardiovascular risk reduction. The concern over statin safety was first raised with the revelation of myopathy and rhabdomyolysis with the use of now withdrawn cerivastatin. Enhanced understanding of the mechanisms behind adverse effects of statins including an insight into the pharmacokinetic properties have minimised fear of statin use among clinicians. Studies reveal that occurrence of myopathy and rhabdomyolysis are rare 1/100000 patient-years. The risk of myopathy/rhabdomyolysis varies between statins due to varying pharmacokinetic profiles. This explains the differing abilities of statins to adverse effects and drug interaction potentials that precipitate adverse effects. Higher dose of rosuvastatin (80 mg/day) was associated with proteinuria and hematuria while lower doses were devoid of such effects. Awareness of drugs interacting with statins and knowledge of certain combinations such as statin and fibrates together with monitoring of altered creatine kinase activity may greatly minimise associated adverse effects. Statins also asymptomatically raise levels of hepatic transaminases but are not correlated with hepatotoxicity. Statins are safe and well tolerated including more recent potent statins such as, rosuvastatin. The benefits of intensive statin use in cardiovascular risk reduction greatly outweigh risks. The present review discusses underlying causes of statin-associated adverse effects including management in high risk groups.

Key words: Myopathy, rhabdomyolysis, safety of statins, statins

Introduction

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) inhibitors belong to the class of lipid-lowering agents that revolutionized pharmacotherapeutics of cardiovascular diseases, leading to a remarkable decline in cardiovascular death and disability in patients with or at risk of developing coronary heart disease (CHD).[1] Batteries of clinical trials have investigated the safety and efficacy of statins in reduction of cardiovascular risks. Most trials proclaimed statins safer and tolerable medicine having considerable risk/benefit ratio with the display of only mild and transient adverse effects such as gastrointestinal symptoms, headache, and rashes.[2] The present review discusses mechanisms and safety of statin-induced adverse effects and their management.

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Search Strategy Used

We identified electronic databases, mainly MEDLINE, HighWire, Cochrane, and Google Scholar for articles from 1990 through November 2011 using keywords "3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) inhibitors or Statins," "Safety of Statins," "Adverse Effects of Statins," "Statin-associated Myopathy," "Renal safety of statins," "Mechanism of Statin-Induced Adverse effects," "Management of Statin-induced Adverse effects." In MEDLINE, we used Medical Subject Heading (MeSH) terms: "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] AND Safety," "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] AND Adverse effects."

Understanding Safety of Statins

Accumulating clinical trial data on safety and efficacy of statins led to framing of guideline by the National

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Cholesterol Education Program and Adult Treatment Panel on use of statins in individuals at high-risk of CHD and other atherosclerotic vascular diseases. High risk patients are prescribed medications for diverse illnesses and often need to take them concurrently leaving enough scope for potential drug-drug interactions, a relevant factor determining the safety profile of statins.[3] Statin possesses differing pharmacological and pharmacokinetic properties and hence differ considerably in safety and has a potential to cause drug-drug interaction. The U.S. Food and Drug Administration (FDA) adverse event report expressed concern over incidence of side-effects, which could be much higher in real clinical situations where patients are not monitored as closely as in clinical trials.[4]

In 2001, the first statin, cerivastatin was withdrawn from market worldwide after confirmed reports of serious myopathy/rhabdomyolysis.[5] The withdrawal sent wave of panic among drug manufacturers and clinicians given the fact that statin by that time had established itself as first-line medicine for reduction of CVD risk. The most important adverse effects associated with statins were asymptomatic increase in hepatic enzymes and musculoskeletal disorders such as myalgia, myopathy, and rhabdomyolysis. Its use caused myalgia in 5% patients, myopathy in 0.1 to 0.2% patients, and rhabdomyolysis in 0.01% patients.[6]

Myopathy

Myopathy or myositis is defined as a diffuse muscle symptom that accompanies elevation of plasma creatine kinase (CK) concentration 10-times higher than the upper limit of normal.[7] It is generally marked by the presence of pain, tenderness, weakness due to severe pain and restriction in mobility. Patients with normal CK levels were also reported to develop myopathic symptoms with statin therapy, indicating that assessment of CK alone cannot adequately predict statin-associated myopathy. Muscle pain in patients taking statins could also occur due to the structural damage of muscle fibers in the absence of elevated CK levels.[8] Though myopathy is a class effect of statins, the potentiality to cause myopathy varies for each statin. In general, these muscular effects have been reported more with the use of synthetic, potent, and more lipophilic statins.[9]

Rhabdomyolysis

Rhabdomyolysis is characterized by marked elevation of CK activity >50-fold, myoglobinemia, myoglobinuria, and myoglobin-induced acute renal failure (oliguria, increased plasma creatinine, potassium, and phosphorus).[10] It is more aggressive and severe form of statin-induced myopathy, resulting in severe skeletal muscle injury, lysis, and excretion of dark brown urine (indicating presence of excess myoglobin release). Rhabdomyolysis alone has been accounted for approximately 10% risk of death due to hyperkalemia-induced arrhythmias or disseminated intravascular coagulation. The risk of rhabdomyolysis was extremely rare and was no more than 5/100000 patient-years.[11] However, considering the prevalence of statin use, even small AE reports would translate into huge health consequences. Patients on lovastatin, simvastatin, and atorvastatin therapy reported higher incidences of rhabdomyolysis. This was due to higher rate of statin metabolism by hepatic microsomal enzymes, cytochrome P3A450 (CYP) isoenzymes. Several commonly prescribed drugs are potent inhibitors of CYP3A4. Concurrent use of statins with these medications increase significantly the risk of rhabdomyolysis as opposed to monotherapy; the risk more often reported in statin-fibrate combination than in statin-niacin combination.[11,12]

Hepatotoxicity

Overall occurrence of statin-induced hepatotoxicity is extremely rare but may be present as asymptomatic elevation of serum transaminases, hepatitis, cholestasis, and acute liver failure (ALF). The mechanism of statin-induced hepatotoxicity is less well-elucidated. Induction of caspase activity, triggering of apoptosis, reduction of coenzyme Q10 (CoQ10), and generation of free radicals have been reported.[13,14] Asymptomatic elevation of hepatic transaminases has been observed in 0.5-2% of patients treated with statins. Statin-induced hepatitis, associated with high levels of transaminases (>3 times the upper limit of normal), hyperbilirubinemia, and clinical symptoms of liver dysfunction was rare and was estimated to be 1/100000 patients-years.[15] Statin-induced ALF was reported to be dose- and time-dependent as reported with other statins, hence making it virtually unpredictable. Potential risk of ALF in vulnerable patients on statin therapy remains unestablished since elevated serum transaminases has no predictive value clinically for ALF.[16] Recently, FDA has recommended revision of labeling instruction for statin and suggested removal of the need for routine periodic monitoring of liver enzymes in patients taking statins. The labels now recommend that liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter. FDA reported serious liver injury with statins to be rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes did not appear to be effective in detecting or preventing serious liver injury. [http://www.fda.gov/Drugs/DrugSafety].

Nephrotoxicity

Most clinical trials reported renoprotective effects of statins, and only few studies reported moderate proteinuria and hematuria with statins.[10,17,18] The dose of

80 mg/day rosuvastatin caused 12% incidence of proteinuria and occasionally hematuria, which led to subsequent withdrawal of this dose. However, a rosuvastatin dose of 10 mg/day for 12 weeks dosage had no effect on total urinary protein excretion, urinary excretion of albumin or immunoglobulin G. rosuvastatin dose of 20 mg/day showed increased α-1 macroglobulin with no deleterious effect along with enhanced glomerular filtration rate.[17] In a study involving 10,289 patients on rosuvastatin and 1,17,102 on other statins, García-Rodríguez and colleagues reported only 2 out of 14 cases of acute renal failures in patients using rosuvastatin. The relative risk of death associated with use of rosuvastatin compared with other statins was reported as 0.55 (95% CI: 0.44-0.68). The authors did not find any evidence of elevated risk of rosuvastatin-induced adverse effects, including nephrotoxicity when compared to other statins. They also did not find any evidence of increased mortality among patients taking rosuvastatin, even after adjustment of age, sex, and prior statin use.[18] Therefore, as a class, statins were reported to be well-tolerated with no known differences in safety. Though myalgia, myopathy, and rhabdomyolysis occur infrequently but were more common in patients with kidney transplant and with chronic kidney disease (CKD).[19] The effect was dose-related and may be precipitated by agents inhibiting CYP-450 isoenzymes. Hence, caution is warranted while co-administering any statin with drugs that metabolize through CYP3A4, particularly fibrates, cyclosporine, and azole antifungals. Given their demonstrated efficacy and safety record coupled with enhanced understanding, statins must be used in the management of patients with established coronary disease but their use in primary prevention of cardiovascular risk warrants caution in dialysis patients who are at greater risk of toxicity and drug interactions. Elderly patients with CKD are at greater risk of adverse drug reactions and, therefore, the lowest possible dose of statins has been suggested for the treatment of hyperlipidemia. The current guidelines state that statins may be used safely in patients with chronic renal diseases and hemodialysis and suggests dose reduction in severe renal impairment.

Other rare adverse effects

In addition to above statin-associated adverse effects, statin causes several other side-effects, which are comparatively insignificant and rare. They have been summarized in Table 1.[10,11,20-27]

Mechanisms of Statin-Induced Adverse Effects

Statin inhibits mevalonate synthesis by inhibiting enzyme HMG-CoA reductase that catalyzes conversion of HMG CoA to mevalonate [Figure 1]. Mevalonate not only acts as precursor of cholesterol but also serves as a precursor for non-steroid isoprenoids such as CoQ10, heme-A, and farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These intermediates of mevalonate pathway impact the benefits as well as risk of statins.[28]

Isoprenoid deficiency

Isoprenoids, FPP, and GGPP are important by-products

Table 1: Other rare adverse effects of statins*

Organ/systems	Statin-induced adverse effects	Reference
Nervous	Hemorrhagic stroke: ↓ LDL-C level → ↑ hemorrhagic stroke; strong data unavailable; risk benefit ratio of statins completely outweighs Peripheral neuropathy: Generally appear after 1-2 months → resolves on discontinuation → low attributable risk Cognitive impairment: Occasionally reported in statin-treated patients → large controlled trials do not confirm Sleep: Sleep disturbances and nightmares	10,11
Cardio-vascular	Vascular reactivity: Statins stimulate vascular CYP2C-derived ROS → inactivation of NO; farnesyl the product of mevalonate cascade deficiency LDL oxidizability: Ubiquinone deficiency → ↑ LDL oxidizability	20
Immune	Induction of apoptosis and release of intracellular antigens (i.e., histones or nucleic acids) → triggers immune response ↑ Auto-antibodies formation → immune response shifts from Th1-mediated (cellular) to Th2-mediated (humoral)	21
Endocrine	Insulin sensitivity: Stimulation of farnesyl and geranylgeranyl transferases both *in vitro* and *in vivo* ↓ Insulin sensitivity and ↑ of plasma insulin concentration after statin therapy Statins impairs insulin signaling and insulin secretion	10
Cancer	Cancer risk: Low coenzyme Q or low serum cholesterol →↑ breast cancer rates	25
Gastrointestinal tract	Rare side-effects: Nausea, dyspepsia, abdominal pain, diarrhea or constipation, gastric ulcer, gallstones	10
Skin	Rare side-effects: Alopecia, rashes, lichenoid eruption, dermographism, chronic urticaria, and toxic epidermal necrolysis	10
Eye	Rarely cause cataract and ocular hemorrhage	26
Reproductive	Rarely cause erectile dysfunction, decrease libido, and gynecomastia	27,28
Blood	↓ Blood clotting → thrombocytopenia and thrombotic thrombocytopenic purpura	29
Respiratory	Rarely cause interstitial lung diseases	30

LDL: Low-density lipoprotein

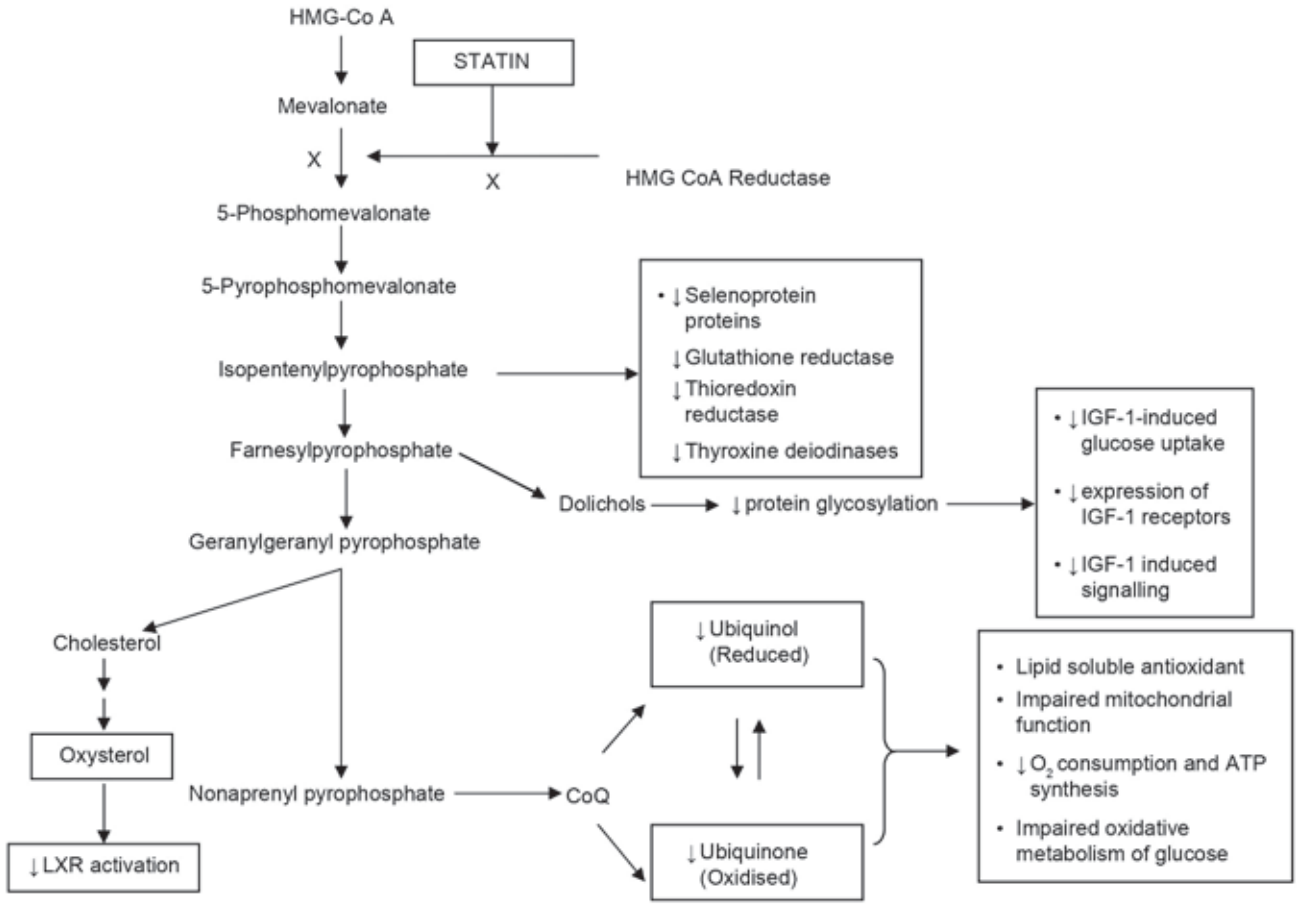

Figure 1: Mevalonate pathway depicting inhibition of downstream intermediate molecules resulting from statin inhibition of mevalonate synthesis. Mevalonate is not only precursor of cholesterol synthesis but also host of other molecules downstream such isopentenylpyrophosphate, farnesylpyrophosphate, geranylgeranyl pyrophosphate, dolichols etc., Statins inhibit HMG-CoA reductase, which catalyzes conversion HMG-CoA to mevalonate. Inhibition of these intermediates leads depletion of various essential molecules cause adverse effects of statins. CoQ: Coenzyme Q; IGF-1: Insulin-like growth factor-1; LXR: Liver X-receptor

of HMG-CoA pathway. These by-products are important component of protein isoprenylation or lipidation, a post-translational modification process where hydrophobic molecules are added to protein and activate them.[9,29] Inhibition of HMG-CoA reductase leads to decreased synthesis of these isoprenoid intermediates affecting protein isoprenylation. Alternatively, statins also promote dysprenylation (protein modification through alternate process). The 2 most important proteins affected are small GTPases and the lamins. Dysprenylation of GTPases ensue a slew of processes, including vacuolation of myofibrils, degeneration and swelling of cellular organelles and ultimately cell death. Reduction of protein isoprenylation also increases cytosolic calcium concentration and activates caspase-3 causing cell death. A role of isoprenoids in statin-induced myopathy was highlighted from the study that reported prevention of apoptosis by isoprenoid administration.[30]

Coenzyme Q

Coenzymes Q (CoQ) consists of 1,4-benzoquinone with a 50-carbon isoprenoid chain derived from FPP. Statin inhibits synthesis of mevalonate, precursor of FPP leading to inhibition of CoQ production. It has also been reported to decrease 20-40% of plasma CoQ10. CoQ10 is a lipid-soluble antioxidant synthesized by mammalian cells and is present as the reduced ubiquinol form and oxidized ubiquinone form (predominant form). It is the only antioxidant capable of regaining its active reduced form upon oxidation. This transition enables CoQ to function as electron carrier in mitochondrial respiratory chain. It acts as cofactor in mitochondrial oxidative phosphorylation and is important for adenosine triphosphate production. Statin-associated myopathy was suggested to result from inhibition of CoQ10 production in mitochondria. CoQ10 deficiency has led to several diseases, including infantile onset multi-systemic diseases, encephalomyopathies with recurrent myoglobinuria, cerebellar ataxia, myopathy, heart failure, Parkinson's disease, and malignancy.[31] It affects children more often than adults. One small clinical trial reported beneficial effect of CoQ10 supplementation in the treatment of statin-induced myopathy.[9]

Sarcolemal cholesterol deficiency

Though still debatable, a deficiency in the level of muscle cell membrane cholesterol has been suggested in alteration of the physical structure of muscle membrane, its integrity, and fluidity. These changes causes an imbalance in the dynamic equilibrium between sarcolemal membrane and plasma cholesterol and hence destabilizes muscle membrane.[32]

Selenoproteins

Selenocysteine synthesis utilizes isopentenylpyrophosphate derived from mevalonate pathway.[10,33] Selenocysteine is required to synthesize selenoproteins such as glutathione peroxidase and thioredoxin reductase (provides antioxidant defense), including thyroxine deiodinases, which catalyzes conversion of thyroxine to triiodothyronine. Statins reduces the availability of isopentenylpyrophosphate, leading to a decrease in production of selenoproteins. Selenium deficiency caused myopathy and cardiomyopathy resembling statin-induced myopathy. Hence, statins-induced deficiency of selenoproteins may impair antioxidant defense and thyroid function.

Dolichols

Dolichols are synthesized from farnesylpyrophosphate and act as carriers for oligosaccharide moiety for protein glycosylation (post-translational modification) required for protein trafficking and function. Statin impairs protein glycosylation by inhibiting dolichol production. One major consequence of statin-induced glycosylation is an impairment of insulin or insulin-like growth factor-1(IGF-1)-induced glucose uptake and proliferation of adipocytes along with reduced expression of glycosylated insulin and IGF-1 receptors and accumulation of unglycosylated receptors in endoplasmic reticulum.[34]

Drug interactions

Statin selectively inhibits HMG-CoA reductase and normally do not show any relevant affinity towards other enzymes or receptors (pharmacodynamic interaction). However, statins show significant pharmacokinetic interaction leading to potential drug-drug interactions.[35] All statins, except pravastatin, are extensively metabolized by liver that involve sets of hepatic microsomal cytochrome P450 isoenzymes. Lovastatin, simvastatin, and atorvastatin are metabolized by CYP3A4; rosuvastatin, and fluvastatin by CYP2C9 isoenzymes; pravastatin through sulfation; and pitavastatin by uridine diphosphate glucuronosyltransferase glucuronidation.[1,9] CYP3A4 isoenzymes are responsible for metabolizing most of the prescribed drugs in the liver. Concomitant use of drug and statin can alter the plasma levels of statins, leading to a risk of myopathy or rhabdomyolysis. However, about 1/3rd of prescriptions for statins are given in combination with drugs with side effects in only 3% of patients.

Both CYP450 inhibitors and inducers play an important role in disposition of statin, in terms of their plasma levels and the risk of statin-induced adverse effects [Table 2].[36] Cytochrome P450 inhibitors are defined as the agents that inhibits the production of the hepatic microsomal enzymes, leading to high plasma levels of statins and greater risk of statin-induced adverse effects like myositis and rhabdomyolysis. Cytochrome P450 inducers are defined as the agents that causes induction of hepatic microsomal enzymes, leading to decrease plasma levels of statins, and hence decreased bioavailability of stain.[1] The common inducers of CYP3A4 isoenzyme were barbiturates, phenytoin, phenobarbital, barbiturates, rifampin, dexamethasone, cyclophosphamide, carbamazepine, omeprazole, and troglitazone, and the common inhibitors were ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic anti-depressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporine A, tacrolimus, mibefradil, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, grapefruit juice, tamoxifen, and amiodarone. The common inducers for CYP2C9 were rifampin, phenobarbital, phenytoin, and troglitazone, and the common inhibitors were ketoconazole, fluconazole, and sulfaphenazole. It is well-known that lipophilic nature of a drug influences its absorption and hydrophilic nature helps in excretion. Most statins are lipophilic in nature, except pravastatin and rosuvastatin; explaining their high safety profile over other statins.

Of CYP450 inhibitors, protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir) are the potent inhibitors of CYP3A4, and its concurrent administration increased plasma statin concentration up to 30-fold; it causes myalgia, rhabdomyolysis, and transaminases elevations.[37] Hence, lovastatin and simvastain are not recommended with PI.

As fluvastatin, pravastatin, rosuvastatin are primarily metabolized by CYP2C9, they are less subject to drug interaction than other statins. In the presence of cyclosporine A, there is 5-23-fold increase in pravastatin bioavailability, leading to reduced biliary clearance of pravastatin and hence increased risk of myopathy. With fluvastatin, cyclosporine A shows milder interaction, which may be due to fluvastatin interaction with CYP2C9.

Intake of grapefruit juice (≥ one liter per day) also increased bioavailability of statins because of the inhibition of intestinal CYP3A4 isoenzyme. The recommended dose for simvastatin and atorvastatin was 10 mg/day, 20 mg/day for lovastatin and 5 mg/day for rosuvastatin due to competition for CYP3A4 when used concurrently with cyclosporine. Similarly, amiodarone dramatically elevated plasma levels of simvastatin levels and, therefore, dose was restricted

Table 2: Safety profiles of statins

Statins	CYP substrate	Cytochrome P3A4		Other interactions
		Inhibitors	Inducers	
Lipophilic statins				
Lovastatin	CYP3A4	Azole antifungals (ketoconazole, itraconazole) Macrolids (erythromycin, clarithromycin, azithromycin) Nefazodone Cyclosporine A Calcium antagonists (mibefradil, diltiazem, verapamil) Protease inhibitors (amprenavir, indinavir etc) Midazolam Mibefradil Grapefruit juice Tamoxifen Amiodarone	Thiazolidenediones anti-diabetic agents	Fibrates Gemfibrozil P-glycoproteins Warfarin
Atorvastatin	CYP3A4	Azole antifungals (ketoconazole, itraconazole) Macrolides (erythromycin, clarithromycin) Nefazodone (anti- depressants) Cyclosporine A Calcium antagonists (mibefradil, diltiazem, verapamil) Protease inhibitors Midazolam Mibefradil Grapefruit juice Tamoxifen Amiodarone	Phenytoin Thiazolidenediones anti-diabetic agents	Fibrates Gemfibrozil P-glycoproteins Digoxin Warfarin
Simvastatin	CYP3A4	Azole antifungals (ketoconazole, itraconazole) Macrolides (erythromycin, clarithromycin) Nefazodone Cyclosporine A Calcium antagonists (mibefradil, diltiazem, verapamil) Protease inhibitors Midazolam Mibefradil Grapefruit juice Tamoxifen Amiodarone	Rifampicin Phenytoin Herbal supplement St. John's wort	Fibrates Gemfibrozil P-glycoproteins Digoxin Warfarin Niacin
Fluvastatin	CYP2C9	Ketoconazole Fluconazole Sulfaphenazole Calcium channel blockers Diclofenac	Rifampin Phenobarbital Phenytoin Troglitazone Thiazolidenediones anti-diabetic agents	Fibrates Niacin Warfarin
Pitavastain	Glucuronidation CYP3A4 and CYP2C9 (minor)	Anti-depressants (nefazodone)	Thiazolidenediones anti-diabetic agents	Fibrates Warfarin
Hydrophilic statins				
Rosuvastatin	CYP2C9 (<10%) and CYP2C 19 (minor)	Ketoconazole Fluconazole Sulfaphenazole	Rifampin Phenobarbital Phenytoin Troglitazone	Fibrates Digoxin Warfarin
Pravastatin	Sulfation	Cyclosporine A		Fibrates Gemfibrozil P-glycoproteins Niacin Warfarin

to 20 mg/day.[9,38] Restrain is warranted in co-prescribing warfarin with statins since fluvastatin and to a lesser extent rosuvastatin are substrates for CYP2C9, which metabolizes warfarin.[38]

Interactions with other agents

Combination of statins and fibrates impairs liver functions, leading to higher levels of statins and hence myopathy. In a study, about 0.12% prevalence of myopathy associated with CK elevations has been found with combination of statins and fibrates.[39] Concurrent gemfibrozil use increased plasma levels of statins by 2-folds.[39] The risk of rhabdomyolysis with gemfibrozil was found to be 10- to 15-fold higher compared to fenofibrate because of differences in fibrate metabolism.[40]

Gemfibrozil-mediated enhancement of myopathic effects was due to competitive inhibition of specific CYP450 and UDP-glucuronosyltransferase (UGT) isoenzymes causing reduced statin clearance. The decrease in statin clearance was due to the competition for glucuronidation, which was required by both statins and fibrates for their metabolism. Statin glucuronidation is an intermediate step in the conversion of active acid forms to lactones and subsequent metabolism by the hepatic CYP450 system.[9]

There was no evidence that niacin and statin combination caused adverse effects greater than risk from individual agents.[1] However, increased risk of myopathy were reported in Chinese population given simvastatin 80 mg/day concurrently with the lipid lowering dose of niacin ≥1 g/day, leading to restriction of simvastatin dose of 40 mg/day in Chinese population on niacin therapy.[41] Statin when given along with ezetimibe increased myopathy.

Transport proteins, P-glycoproteins leads to low bioavailability of atorvastatin, lovastatin, simvastatin, pravastatin, leading to rhabdomyolysis.[1] Co-administration of atorvastatin (80 mg/day) and digoxin (0.25 mg/day) for 20 days increased exposure to digoxin by inhibition of P-glycoproteins.

Management of statin-induced adverse effects

Literature clearly documented increased risk with higher doses and serum concentrations of statins. The reported prevalence of statin-associated adverse effects are less, and among all the available statins, rate of fatal rhabdomyolysis was reported to be less than 1 death/million prescriptions.[42] The National Lipid Association (NLA) Statin Safety Task Force[5] published guidelines regarding the management of statin-associated adverse effects briefly summarized in Table 3.

High Risk/Vulnerable Population to Statin Adverse Effects

Statins are mostly safe, but certain population groups are at an elevated risk of developing statin-associated adverse effects and in whom careful monitoring of statins is recommended.

Alcoholics

There is lack of literature documenting prevalence of statin myopathy among alcoholics; however, excess alcohol intake has been a risk factor for rhabdomyolysis induced by pressure necrosis.[43] In the Heart Protection Study, no upper limit for alcohol consumption was set till the time liver function tests remained within an acceptable range.[44]

Pregnant women

Statins have been contraindicated in pregnancy.[44] Premenopausal women treated with statins were asked to avoid pregnancy or if they so intend, should to stop statin therapy. There have been reports of statins inducing teratogenicity and have caused congenital abnormalities in the babies of women who took statins during early pregnancy. However, further prospective clinical trial collection of data could ascertain further teratogenic potentials of statins.[45,46]

Patients on warfarin

Statins such as simvastatin, fluvastatin, and rosuvastatin

Table 3: Management of statin-associated adverse effects

Muscle effects	NLA does not recommend CK measurement before statin therapy unless individual is at high risk Routine CK measurement in asymptomatic patients → not recommended Counseling patients on the risk of statin myopathy in symptomatic patients, CK levels should be measured CK levels <10 times the ULN: Statin therapy may be continued or dose titration with close monitoring required CK level >10 times or 10,000 IU/L the ULN: IV hydration therapy, monitoring of renal function and initiation of treatment for rhabdomyolysis recommended CK levels <5 times the ULN → decision to continue statin therapy → based on symptom tolerability; in intolerable case, stopping of statin therapy or reinstitution of therapy with alternate agent or with lower dose once asymptomatic In case symptoms rebound → alternate therapy should be considered
Hepatic effects	Hepatic transaminases assessment → before initiation and 12 week after initiation of insulin therapy and Periodical check up Measurement of transaminase levels, fractionated bilirubin level and LFT → any overt signs of liver toxicity, such as jaundice, malaise, fatigue, and lethargy Transaminase levels between 1 and 3 → In asymptomatic individuals, statin therapy continued with close follow up testing Transaminase levels >3 times ULN → Reduction of statin dose or discontinuation of statin therapy while ruling out other causes In case of objective evidence of liver injury → Discontinuation of statin therapy and referring patient to gastroenterologist
Renal effects	Regular assessment of serum creatinine and proteinuria → not needed for patients on statin therapy Baseline creatinine levels at the initiation of statin therapy → may help to identify patients with underlying kidney disease in high risk patients Adjustment in statin doses is recommended → In case of increases in creatinine levels while on statin therapy In case of proteinuria detection → consider dose adjustment Any abnormal renal indices → assessment of causes other than statin may be looked for CKD patients → statin may be administered with close monitoring; dose adjustment in moderate to severe kidney diseases

CK: Creatine kinase, ULN: Upper limit of normal, LFT: Liver function test, CKD: Chronic kidney disease

have been reported to potentiate the anticoagulant effect of warfarin.[47] People requiring warfarin should check their anticoagulation control while initiating, stopping, or modifying statin therapy. However, the change in the required dose of warfarin is small, but occasionally patients may experience clinically relevant changes to their anticoagulant control.

Geriatric patients

Statins have demonstrated benefits in geriatrics in those with CHD and diabetes mellitus.[48] Future studies exploring statin efficacy in primary prevention for patients older than 75-80 years are needed along with better risk assessment tools. From a benefit risk perspective, the benefits of statin therapy in the elderly clearly outweighed the low risk of serious side effects. However, randomized trial data have shown that lowering cholesterol no longer extended life in the elderly, even those at high risk of heart disease. The elderly may be more vulnerable to known adverse effects, and evidence provides cause for concern that new risks may supervene, including cancer, neurodegenerative disease, and heart failure. The impact of statin adverse effects (e.g., muscle and cognitive problems) may be amplified in elderly, and even modest lowering of cognitive and physical function in older elderly may portend increased disability, hospitalization, institutionalization, and mortality.[49] No dose adjustment was recommended despite the fact that geriatrics may be at higher risk of developing myopathy. In randomized trials that included people above 80 year of age, the safety profile and relative benefits of statin treatment have been reported to be similar to those in young adult people. Recent literatures indicate the benefits of statin therapy in the elderly, which outweigh the low risk of serious side effects, still the use of statins in the elderly should be undertaken with circumspection and close scrutiny for any possible adverse effects.

Pediatric patients

There are limited, short-term data demonstrating that statins are apparently safe in children, though long-term follow-up is completely lacking.[50] At an 8 years of age, a child's brain and other organ systems remain in dynamic stages of growth and development, which considerably raise concern that long-term pharmacotherapy initiated at this age may adversely affect the central nervous system, immune function, hormones, energy metabolism, or other systems in unanticipated ways. Recent research suggested that increasing body weight in childhood, even within the range considered normal, was strongly associated with the risk of cardiovascular disease in adulthood.[51] The PLUTO (Pediatric Lipid-redUction Trial of rOsuvastatin) study involving adolescents, age 10 to 17 years along with other studies in nearly 1,000 pediatric patients confirmed that LDL-C lowering with statins was well tolerated in adolescents with familial hypercholesterolemia (FH).[52]

The present body of literatures on statin use in pediatric patients revealed that statins are effective at lowering LDL and TC levels and are fairly well-tolerated for the short-term period in children; therefore, currently an appropriate choice for use in FH as outlined by the clinical report and possibly for other childhood dyslipidemia with elevated TC and LDL levels after lifestyle modifications have been unsuccessful. However, appropriate monitoring of drug adverse effects and growth and development should occur in all patients.[53]

Cardiac patients

Some reports noted harmful effects of statins in patient with cardiac failure since it was observed that low cholesterol are associated with poor outcome in such patients.[54] One large study showed high levels of N-terminal pro-B type natiuretic peptide (N-BNP), which was predictive of cardiac failure, received similar cardiovascular benefits with simvastatin compared with patients without cardiovascular hazard.[55]

Kidney function

Although statins are considered safe in moderate renal impairment, but patients having glomerular filtration rate in the range of 30-60 mL/min were at a higher cardiovascular risk. Data suggests statins beneficial in these subgroups, but they may be at a higher risk of myopathy. One trial showed no cardiovascular benefits with atorvastatin 20 mg/day in patients with diabetes on maintenance hemodialysis; therefore, role of statins for the prevention of cardiovascular disease in patients with chronic kidney disease is less well-understood).[56]

A meta-analysis of 36 studies that included 40,600 participants assessed the effects of rosuvastatin on the renal safety. The study suggested that intensive LDL-C-lowering treatment with rosuvastatin did not affect the risk of developing renal insufficiency or renal failure in patients who do not have advanced, pre-existing renal disease.[57] The study supported that rosuvastatin may be safely used in renal-compromised patients.

Increasing Safety of Statins

Statins may be classified into 3 categories based on their increasing potency and efficacy in lowering plasma low-density lipoprotein cholesterol (LDL-C) concentration. The first generation statins included lovastatin, pravastatin, and fluvastatin; simvastatin and atorvastatin among second

generation; and rosuvastatin and pitavastatin among third generation statins.

First generation statins

The first generation statins (FGS) were introduced during the late 1980s and 1990s, and this class of statins had the lowest potency. Among FGS, pravastatin was the most studied statin, and several clinical trials showed reduction in LDL-C levels, cardiac mortality, and coronary events.[58] In secondary prevention and symptomatic coronary disease patients too, pravastatin was proved to be effective. Though the adequate evidence is lacking, lovastatin and fluvastatin also demonstrated benefited cardiovascular risk reduction. In the FGS, pravastatin and fluvastatin commanded much attention because of their low drug interaction as they are not metabolized by CYP450 isoenzyme systems. Hence, in spite of their low potency, they are used as an alternative in patients who are intolerant to potent statins.

Second generation statins

The second generation of statins (SGS) was marked by introduction of atorvastatin and simvastatin. Even today, they are considered as the best selling statins. These statins had superior efficacy in lowering plasma LDL-C levels than FGS. The daily doses of only 10 mg atorvastatin and 20 mg simvastatin caused greater than 30% lowering of LDL compared with 20-40 mg daily doses of FGS. Battery of trials demonstrated their use in both primary and secondary trials. Trials to study intensive versus moderate statin therapy for maximizing LDL-C lowering and to achieve better cardiovascular outcomes would be possible only with the availability of more potent and superior SGS. Intensive statin therapy was mostly directed at secondary prevention patients who mostly were benefited from aggressive lipid-lowering agents. The pharmacological demonstration of atorvastatin and simvastatin drug-drug interaction is now well-established and had raised many eyebrows in the use of SGS in high-risk patients. However, various clinical trials demonstrated adequate safety and efficacy of aggressive lipid-lowering in high-risk patients with SGS.[59-62] Wider information on statin drug interactions and monitoring of the statin adverse effects would further help in minimizing statin-induced myopathy.

Third generation statins (rosuvastatin)

Third generation statins (TGS) included rosuvastatin and pitavastatin, which had high potency and efficacy and thus termed as super statins.[58] Rosuvastatin owes remarkable potency and efficacy due to its fluorinated phenyl group and hydrophilic methane sulphonamide group in addition to the common dihydroxyheptenoic acid side chain. Its unique chemical structure enables multiple and strong binding with HMG-CoA reductase enzyme. It has low drug interaction potential due to its hydrophilic nature, which avoids biotransformation for conversion into water-soluble intermediates for elimination.[62] Pitavastatin also have several clinical advantages over FGS and SGSs. It's lowering potentiality of serum LDL-C was greater than pravastatin but was similar to atorvastatin. It is primarily metabolized through glucuronidation, and only minor fractions are metabolized by CYP2C9 and CYP3A4. Therefore, pitavastatin is hardly metabolized by microsomal cytochrome P450 system compared to other statins and hence has an advantage of not having unexpected interactions with other drugs. These TGSs are used as an alternative to other statins in high-risk patients who more often develop statin intolerance.

Conclusion

Almost all the statin trials reported statins to be safe and tolerable. However, in the August 2001, withdrawal of cerivastatin caused widespread ripples among clinicians because of their wide usage in reduction of cardiovascular morbidity and mortality. The revelation that statins may cause fatal rhabdomyolysis raised questions on the safety of statin. Later, several clinical trials dispelled this notion, and the current guidelines suggested dose reduction and halting of statin therapy only in extreme conditions. Subsequent to the rise of safety issues, new potent statins such as rosuvastatin has been scrutinized regarding high dose (80 mg/day) that caused proteinuria and hematuria. However, these effects were transient and reversible, requiring just the reduction of the dosage. The understanding of relatively common statin-associated adverse effects will enable clinicians in making decision in choosing out appropriate statin for their patients giving due consideration to the fact that benefits of statins greatly outweigh its risks.

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Rosuvastatin Does Not Affect Fasting Glucose, Insulin Resistance, or Adiponectin in Patients with Mild to Moderate Hypertension

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The effects of statins on insulin resistance and new-onset diabetes are unclear. The purpose of this study was to evaluate the effects of rosuvastatin on insulin resistance and adiponectin in patients with mild to moderate hypertension. In a randomized, prospective, single-blind study, 53 hypertensive patients were randomly assigned to the control group (n=26) or the rosuvastatin (20 mg once daily) group (n=27) during an 8-week treatment period. Both groups showed significant improvements in systolic blood pressure and flow-mediated dilation (FMD) after 8 weeks of treatment. Rosuvastatin treatment improved total cholesterol, low-density lipoprotein (LDL)-cholesterol, and triglyceride levels. The control and rosuvastatin treatment groups did not differ significantly in the change in HbA1c (3.0±10.1% vs. -1.3±12.7%; p=0.33), fasting glucose (-1.3±18.0% vs. 2.5±24.1%; p=0.69), or fasting insulin levels (5.2±70.5% vs. 22.6±133.2%; p=0.27) from baseline. Furthermore, the control and rosuvastatin treatment groups did not differ significantly in the change in the QUICKI insulin sensitivity index (mean change, 2.2±11.6% vs. 3.6±11.9%; p=0.64) or the HOMA index (11.6±94.9% vs. 32.4±176.7%; p=0.44). The plasma adiponectin level increased significantly in the rosuvastatin treatment group (p=0.046), but did not differ significantly from that in the control group (mean change, 23.2±28.4% vs. 23.1±27.6%; p=0.36). Eight weeks of rosuvastatin (20 mg) therapy resulted in no significant improvement or deterioration in fasting glucose levels, insulin resistance, or adiponectin levels in patients with mild to moderate hypertension.

Key Words: *Hydroxymethylglutaryl-CoA reductase inhibitors; Insulin resistance; Adiponectin; Blood glucose*

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INTRODUCTION

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are prescribed worldwide in patients with or at risk for cardiovascular disease (CVD). Reduction of low-density lipoprotein (LDL) cholesterol is one of the primary mechanisms of CVD prevention. Beyond the lipid-lowering effect of statins alone, there is abundant evidence showing that statins provide immediate benefits, the so-called pleiotropic effects of statins. These pleiotropic effects are thought to include improved endothelial function, enhanced stabilization of atheromatous plaque, decreased oxidative stress, decreased vascular inflammation, and a decrease in the probability of developing atherosclerotic events in metabolic syndrome, type 2 diabetes, and hypertension.[1-6] These effects of statins may consequently prevent plaque rupture and subsequent myocardial infarction in the proinflammatory and prothrombotic environment.[7,8] Recently, randomized controlled clinical trials have raised the concern that lipophilic statins might have unfavorable metabolic effects, such as reducing insulin secretion and exacerbating insulin resistance and the development of new-onset diabetes.[3,9,10] Another study also showed that atorvastatin treatment resulted in significant increases in fasting insulin and glycated hemoglobin (HbA1C) levels consistent with insulin resistance in hyper-

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cholesterolemic patients.[11] These concerns are very important because insulin resistance increases the risk of CVD. Although some studies have been published on the adverse effects of statins, their effects on insulin resistance and new-onset diabetes are not obvious.[3,6,11,12]

The purpose of this study was to evaluate the effects of rosuvastatin on insulin resistance and adiponectin in patients with newly diagnosed mild to moderate hypertension.

MATERIALS AND METHODS

1. Patients and methods

This study was a randomized, prospective, single-blind study in patients with mild to moderate hypertension [systolic blood pressure (BP)<170 mmHg or diastolic BP <105 mmHg] from September 2009 to April 2010. The study was carried out in Gwangju Veterans Hospital and was approved by the institutional review board of the hospital. Every patient was given full information about the study objectives and methods and signed a written informed consent form. No patient had taken any lipid-lowering agent, hormone therapy, or vitamin supplements during the 8 weeks before randomization. Also, during the pre-randomization period (8 weeks) and the study period, to make the comparison of insulin sensitivity fair in the two groups, all patients took an angiotensin type II receptor blocker (ARB), telmisartan 80 mg, followed by a calcium channel blocker for the treatment of hypertension. Patients with newly diagnosed mild to moderate hypertension were included. We excluded patients with renal disease, hepatic disease, any thyroid disease, uncontrolled diabetes (HbA1C>8%), uncontrolled severe hypertension, stroke, acute coronary syndrome, and unstable angina.

After a 1-week screening period, 57 patients were randomly assigned to either placebo (Group I: mean, 61.5±6.9 years, n=26) or rosuvastatin 20 mg (Group II: mean, 60.4±7.2 years, n=27) once daily during a 2-month treatment period. The allocation was performed by using envelopes. At screening, 57 patients were enrolled in the study. One patient was diagnosed with hepatocellular carcinoma. Three patients withdrew their informed consent. Thus, the final analysis was performed on 53 patients (Fig. 1).

The patients were examined at baseline and at 8-week follow-up visits to assess changes in fasting glucose, insulin, HbA1C levels, QUICKI (quantitative insulin-sensitivity check index), HOMA (homeostasis model assessment), adiponectin, and flow-mediated vasodilation (FMD).

2. Measurement of blood pressure

For BP measurement, stabilization was attempted for more than 10 minutes. BP was measured on the right upper arm with the patient in a sitting position. The measurement was performed at least 2 times at a minimum interval of 10 minutes and the measurements were averaged. Systolic BP of more than 140 mmHg or diastolic pressure of more than 90 mmHg was defined as hypertension.

3. Evaluation of vascular endothelial function

The evaluation of vascular endothelial function was performed by FMD, a noninvasive method. To ensure that the ultrasonographic findings of the brachial artery were detected, the most accessible area, which was 2 to 5 cm inferior to the antecubital fossa, was targeted by use of a high-resolution ultrasonography unit (Sequoia 512; Acuson, Mountain View, CA, USA) to which a 10 MHz linear array transducer was implanted. Ultrasonography was performed according to methods reported previously.[13,14]

4. Insulin resistance and adiponectin measurement

Blood sampling was done in the morning before treatment and after 8 weeks of drug administration and more than 8 hours of fasting. Plasma insulin was measured with a radioimmunoassay (Biosource Inc., Nivelles, Belgium), as was adiponectin (LINCO Research Inc., St. Louis, MO, USA). Indices for insulin sensitivity (QUICKI and HOMA) were calculated on the basis of the following formulas: QUICKI=1/{log (insulin)+log (glucose)} and HOMA=fasting insulin × fasting glucose/22.5. The units of measurement of insulin and glucose were μU/ml and mg/dl, respectively.

5. Statistical analysis

All data are expressed as the mean±SD. We used Student's paired *t* test or Wilcoxon signed rank test to compare values between baseline and treatment at 2 months. A comparison of the measurements between the two groups was made by using repeated-measures ANOVA. The mean delta change (%) was calculated as a mean of delta

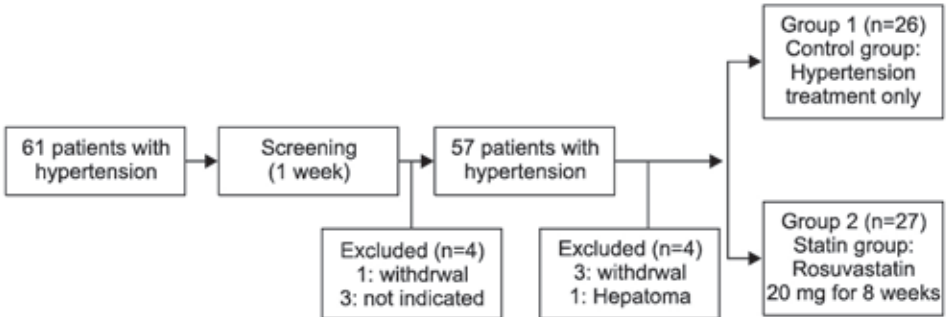

FIG. 1. Flow chart of the study.

change=(baseline value − follow-up value)/baseline value × 100 (%). All statistical procedures were performed with the Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS Inc., Chicago, IL, USA). A $p<0.05$ was considered statistically significant.

RESULTS

The baseline characteristics of the subjects are shown in Table 1. No significant differences existed between the two treatment groups. There were 48 men and 5 women; the patients' mean age was 60.7±6.8 years. Fourteen of the patients had type 2 diabetes. None of the patients experienced any drug-related complications during the 8 weeks of treatment.

Both groups showed significant improvements in systolic blood pressure (control group, from 153.4±14.7 mmHg to 137.9±14.3 mmHg; rosuvastatin group: from 154.4±14.3 mmHg to 132.8±13.8 mmHg; $p<0.01$) and FMD (control group, from 7.5±3.1% to 9.9±2.9%; rosuvastatin group, from 7.8±3.5% to 10.5±3.6%; $p<0.01$) after 8 weeks compared with baseline. However, there were no significant differences between the two groups after 8 weeks of treatment (Table 2). The control group did not show significant changes in the lipid profile, but the rosuvastatin group showed improvement in total cholesterol (from 218.2±36.9 mg/dl to 167.1±43.0 mg/dl; $p<0.01$), LDL-cholesterol (from 147.5±33.3 mg/dl to 101.8±32.4 mg/dl; $p<0.01$), and triglycerides (from 174.0±61.9 mg/dl to 136.8±64.6 mg/dl; $p<0.01$; Table 2). Neither group showed a significant change in the high-sensitivity C-reactive protein level from baseline to 8 weeks.

There were no significant differences in fasting glucose, fasting insulin, QUICKI, HOMA, or adiponectin levels between the two groups before or after randomization (Table 2). The mean delta changes in HbA1c (3.0±10.1% vs. −1.3±12.7%; p=0.33), fasting glucose (−1.3±18.0% vs. 2.5±24.1%; p=0.69), and fasting insulin levels (5.2±70.5% vs. 22.6±133.2%; p=0.27) in the control and rosuvastatin treatment groups were not significantly different (Fig. 2).

TABLE 1. Baseline characteristics of the subjects in the two groups

	Control (n=26)	Rosuvastatin (n=27)	p value
Age (years)	61.5±6.9	60.4±7.2	0.40
Sex, M/F (%)	23/3 (88/12)	25/2 (93/7)	1.00
Body mass index			
Height (cm)	167.2±6.9	165.7±4.5	0.38
Body weight (kg)	66.8±7.4	69.7±8.2	0.18
BMI (kg/m^2)	24.0±2.7	25.4±2.6	0.63
Smoking (%)	14 (53.8)	15 (55.6)	0.63
Associated disease			
Diabetes (%)	5 (19.2)	6 (22.2)	1.00
Dyslipidemia (%)	6 (23.0)	7 (25.9)	0.87
Medication			
CCB (%)	50.0	53.8	1.00
Aspirin (%)	46.2	53.8	0.78
ARB (%)	100	100	1.00
Insulin (%)	0	0	1.00
Sulfonylurea (%)	53.8	46.2	0.78
Metformin (%)	55.6	55.6	1.00

BMI: body mass index, CCB: calcium channel blocker, ARB: angiotensin receptor.

TABLE 2. Comparison of lipid and endocrine parameters between the control and rosuvastatin groups

Variables	Control (n=26)		Rosuvastatin (n=27)	
	Baseline	Treatment	Baseline	Treatment
Lipid profile (mg/dl)				
Total cholesterol	198.9±36.4	195.7±35.9	218.2±36.9	167.1±43.0*
Triglyceride	204.1±125.0	154.4±105.8	174.0±61.9	136.8±64.6*
HDL cholesterol	49.8±14.0	50.1±11.8	50.2±10.3	50.6±12.7
LDL cholesterol	127.0±31.7	128.9±34.4	147.5±33.3	101.8±32.4*
hs-CRP (mg/l)	1.61±2.3	1.7±2.1	1.89±2.7	1.7±2.1
HbA1C (%)	6.0±1.2	6.0±1.4	6.0±1.0	5.7±0.6
Insulin resistance				
Glucose (mg/dl)	112.5±34.5	105.6±27.8	107.6±27.6	105.0±25.3
Insulin (uU/ml)	6.0±4.4	5.1±3.5	8.0±6.0	8.2±10.2
QUICKI	0.38±0.06	0.39±0.55	0.36±0.05	0.37±0.55
HOMA	3.2±3.0	2.5±2.1	3.6±2.6	2.9±2.1
Adiponectin (ug/ml)	7.2±1.8	8.9±2.2*	7.1±2.9	8.7±2.3*
Blood pressure				
Systolic BP (mmHg)	153.4±14.7	137.9±14.3*	154.4±14.3	132.8±13.8*
Diastolic BP (mmHg)	88.2±13.8	84.4±8.4	89.3±11.5	82.7±9.2*
FMD (%)	7.5±3.1	9.9±2.9*	7.8±3.5	10.5±3.6*

*$p<0.05$ comparison with each baseline value. HDL: high-density lipoprotein, LDL: low-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, HbA1C: glycated hemoglobin, QUICKI: quantitative insulin-sensitivity check index, HOMA: homeostasis model assessment, BP: blood pressure, FMD: flow-mediated vasodilation.

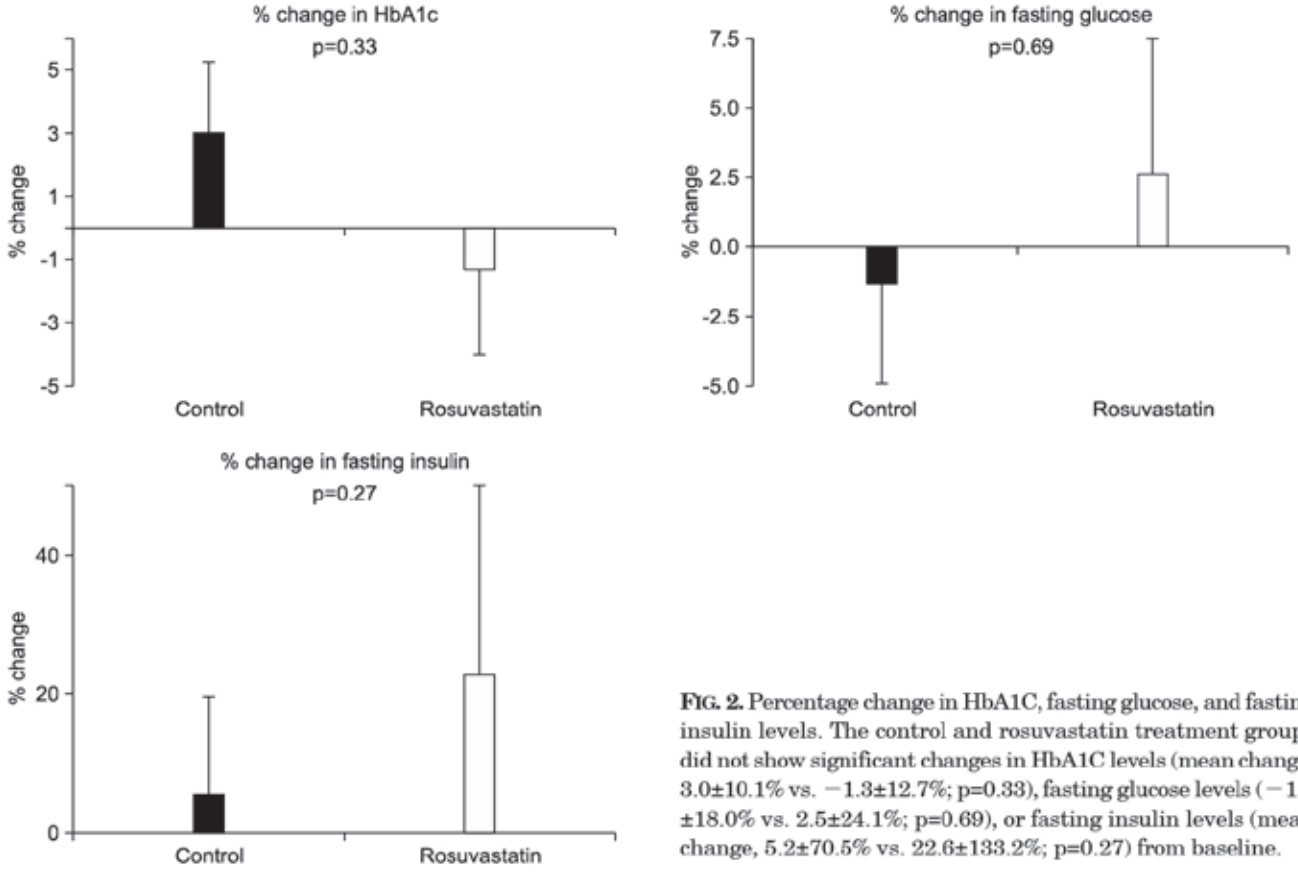

FIG. 2. Percentage change in HbA1C, fasting glucose, and fasting insulin levels. The control and rosuvastatin treatment groups did not show significant changes in HbA1C levels (mean change, 3.0±10.1% vs. −1.3±12.7%; p=0.33), fasting glucose levels (−1.3 ±18.0% vs. 2.5±24.1%; p=0.69), or fasting insulin levels (mean change, 5.2±70.5% vs. 22.6±133.2%; p=0.27) from baseline.

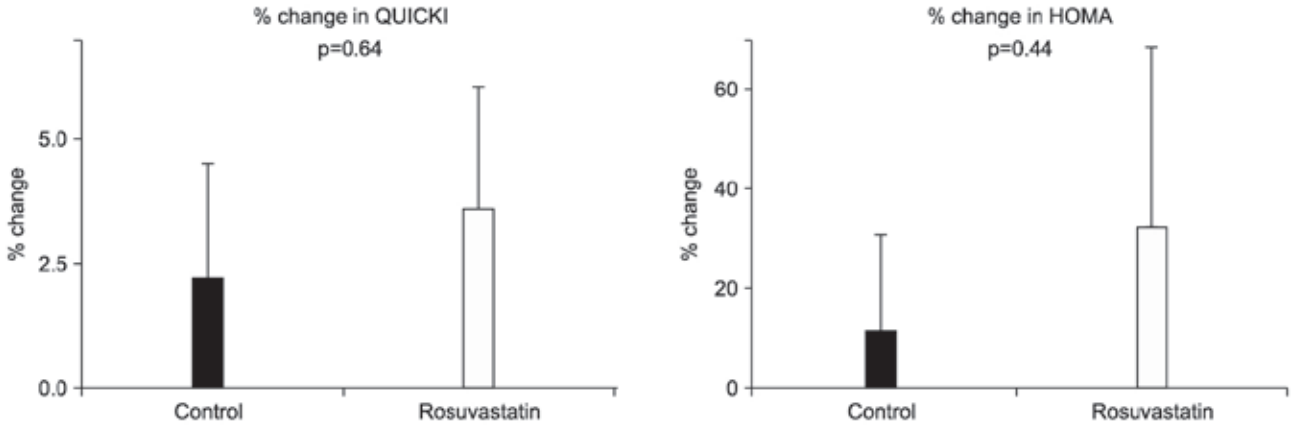

FIG. 3. Percentage change in QUICKI and HOMA indices. The control and rosuvastatin treatment groups did not show significant changes in the QUICKI index (mean change, 2.2±11.6% vs. 3.6±11.9%; p=0.64) or the HOMA index (11.6±94.9% vs. 32.4±176.7%; p=0.44). QUICKI: Quantitative Insulin-Sensitivity Check Index, HOMA: Homeostasis Model Assessment.

Furthermore, the mean delta changes of the QUICKI (2.2±11.6% vs. 3.6±11.9%; p=0.64) and HOMA index (11.6±94.9% vs. 32.4±176.7%; p=0.44) also were not significantly different between the control and rosuvastatin groups (Fig. 3). The plasma adiponectin level increased significantly in both groups compared with baseline. However, there was no significant difference in the mean delta change between the control and rosuvastatin groups (23.2±28.4% vs. 23.1±27.6%; p=0.36; Fig. 4).

DISCUSSION

The current study showed that 8 weeks of rosuvastatin (20 mg daily) therapy resulted in no significant improvement or deterioration in fasting glucose levels, adiponectin levels, or insulin resistance. As expected, all components of the lipid profile improved more from baseline following rosuvastatin treatment than control treatment. Our results suggest that rosuvastatin did not cause glucose intol-

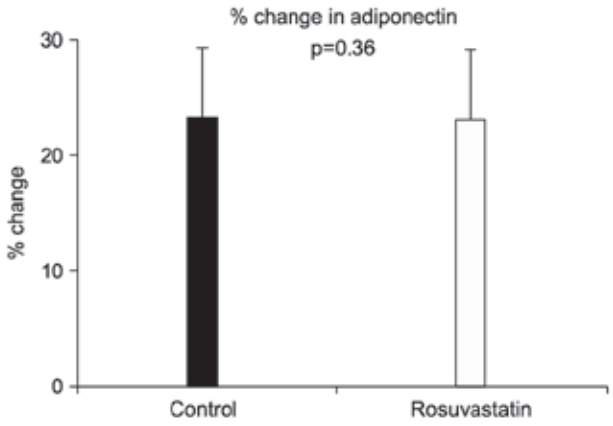

FIG. 4. Percentage change in adiponectin level. The adiponectin level significantly increased in the rosuvastatin group (p=0.046) but showed no significant difference compared with the control group (mean change, 23.2±28.4% vs. 23.1±27.6%; p=0.36).

erance or insulin resistance.

Insulin resistance is associated with increased risk for CVD.[15,16] The association between insulin resistance and hypertension is controversial. Whereas some studies have reported that insulin resistance is strongly related to hypertension, others have shown only a weak or even no association.[17-19] In clinical practice, risk factors for CVD tend to cluster within individuals, and hypertensive patients are at increased risk for metabolic syndrome and adverse changes in insulin resistance and the lipid profile. For risk modification, statins are prescribed in patients with multiple risk factors for CVD.

Recent clinical studies have demonstrated that lipophilic statins, such as atorvastatin, simvastatin, and the hydrophilic statin rosuvastatin might increase the onset of new diabetes.[3,9,10] However, these studies were not designed to evaluate the onset of new diabetes or insulin resistance. Therefore, these results are not clear and have not led to recommendations for the general population. Other researchers have previously reported that simvastatin reduces adiponectin levels and insulin sensitivity.[20] Previously, Koh et al.[11] published that atorvastatin treatment in healthy hyperlipidemic patients aggravates insulin resistance by increasing fasting glucose, insulin, and HbA1c levels at relatively high doses. The characteristics of the patients in both studies were similar. The baseline characteristics, such as lipid level, proportion of diabetic patients, and laboratory findings of baseline insulin resistance were similar, even though the patient group in that study was composed of healthy volunteers and our patient group consisted of newly diagnosed hypertensive, dyslipidemic patients.[11] Indeed, whether statins, especially atorvastatin, have a decisive effect on insulin resistance is unclear. Recently, Koh et al.[21] published that compared with pravastatin, rosuvastatin therapy significantly increased fasting insulin and HbA1c while decreasing plasma adiponectin levels and the QUICKI index compared

First, our patients simultaneously took telmisartan 80 mg, which has a PPAR-γ effect that improves insulin resistance. As a result, it follows that it may have had some masking effects. This is a limitation of our study protocol. Second, our study groups consisted of hypertensive, dyslipidemic patients and included some patients with diabetes. Our patients already had metabolic disease. Thus, the unwanted metabolic effect by rosuvastatin may have been relatively weaker than in the patients in Koh et al.'s study.

Huptas et al.[6] showed that 6 weeks of atorvastatin treatment results in significant improvement in insulin sensitivity in patients with metabolic syndrome. But, these conflicting results cannot be explained. Furthermore, it is unknown whether different statins have different metabolic effects on the basis of their lipophilic properties. Similar findings were shown for pravastatin, which is non-lipophilic.[22,23] Another study compared the effects of atorvastatin (10 mg) and rosuvastatin (10 mg) on changes in glucose and insulin levels, and the HOMA of the insulin resistance index, which were not significantly different between the two groups.[24] Also, the result of a meta-analysis of randomized controlled trials may suggest that potential differences exist between statins.[25] It is not clear why various statins have beneficial metabolic actions in some studies, but not in others. Thus, further head-to-head comparative studies are needed to elucidate the effects of statins on glucose metabolism.

Our results showed that lipid levels improved, adiponectin levels increased, and the percentage change in fasting glucose and insulin levels and the QUICKI and HOMA indexes were not significantly different between the rosuvastatin and control treatment groups. To determine the trends in each group's differences according to treatment, we assessed the mean value of each parameter and the mean of the delta change. The values shown in Table 2 and the mean change percentages (Fig. 2-4) for each parameter may seem to be different results. But this could be because of the statistical differences. Studies in an animal model of insulin resistance suggested that rosuvastatin treatment increases whole-body and peripheral tissue insulin sensitivity via improved cellular insulin signal transduction.[26] A 20 mg dose of rosuvastatin, which is a relatively high dose, was used in our study. Rosuvastatin (20 mg) has equal lipid-lowering potency as atorvastatin (40 mg). Therefore, we assume that each statin has differential effects on insulin sensitivity and the rate of new-onset diabetes according to dosage.

The rosuvastatin (20 mg) group tended to show improved vascular endothelial function and FMD, but showed no significant difference at the time of study termination. Our study and another study showed that treatment with a statin improved FMD in patients with a decreased baseline FMD.[27] In that study, discontinuation of statin treatment reversed the improved FMD to baseline.[27] The results showed that statins definitely affect vascular endothelial

cular disease risk factors. In the current study, most patients had low cardiovascular disease risk factors; the anti-hypertensive ARB therapy could have already resulted in maximum improvement of vascular endothelial function. Under such conditions, statins would not have an additional effect on vascular endothelial function owing to the ceiling effect. If the current study had enrolled more patients with diabetes, metabolic syndrome, or other cardiovascular disease, the results would possibly have greater meaning.

In our data, the value of adiponectin increased in both groups but did not differ significantly between the two groups. Some diabetic patients were included in this study, because many hypertensive patients already show metabolic disease in the real world. As a natural consequence, it follows that analysis of our data was partially ambiguous. Furthermore, telmisartan 80 mg, which has a PPAR-γ effect that improves insulin resistance, was taken by all patients for adequate BP control. As a result, it follows that the ARB may have shown good BP control but some masking effects on adiponectin, inflammatory markers, and insulin resistance.

In conclusion, our study showed that 8 weeks of rosuvastatin (20 mg daily) therapy showed no significant improvement or deterioration of fasting glucose levels, insulin resistance, and adiponectin levels in newly diagnosed hypertensive patients treated with the ARB telmisartan.

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* For original article with references please visit:
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Comparison of Rosuvastatin Versus Atorvastatin for Coronary Plaque Stabilization

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Statins are widely used to lower cholesterol and to reduce cardiovascular events. Whether all statins have similar effects on plaque stabilization is unknown. We aimed to investigate coronary plaque response to treatment with different statins that result in similar lipid reduction using serial multimodality intracoronary imaging. Patients with de novo coronary artery disease requiring intervention were randomized to rosuvastatin 10 mg (R10) or atorvastatin 20 mg (A20) daily. Optical coherence tomography and intravascular ultrasound were performed at baseline, 6 months, and 12 months. Untreated nonculprit plaques were analyzed by optical coherence tomography for thin-cap fibroatheroma, minimum fibrous cap thickness, lipid arc, and lipid length. Total and percent atheroma volume, respectively were analyzed by intravascular ultrasound. Forty-three patients completed the protocol (R10: 24 patients, 31 plaques; A20: 19 patients, 30 plaques). The decrease in serum lipids was similar. From baseline to 6 months to 12 months, minimum fibrous cap thickness increased in the R10 group (61.4 ± 15.9 μm to 120.9 ± 57.9 μm to 171.5 ± 67.8 μm, p <0.001) and the A20 group (60.8 ± 18.1 μm to 99.2 ± 47.7 μm to 127.0 ± 66.8 μm, p <0.001). Prevalence of thin-cap fibroatheroma significantly decreased in the R10 and A20 groups (−48% and −53%, respectively, p <0.001 for intragroup comparisons). Only the R10 group had a decrease in macrophage density (−23%, p = 0.04) and microvessels (−12%, p = 0.002). Total atheroma volume decreased in the R10 group (109.2 ± 62.1 mm^3 to 101.8 ± 61.1 mm^3 to 102.5 ± 62.2 mm^3, p = 0.047) but not in the A20 group (83.3 ± 48.5mm^3 to 77.6 ± 43.0 mm^3 to 77.9 ± 48.6 mm^3, p = 0.07). In conclusion, although both statins demonstrated similar reductions in lipid profiles, the rosuvastatin group showed more rapid and robust plaque stabilization, and regression of plaque volume compared to the atorvastatin group. **(Am J Cardiol 2019;123:1565−1571)**

The majority of acute coronary syndromes (ACS) are due to the rupture of vulnerable atherosclerotic plaques.[1,2] Features of plaque vulnerability include thin fibrous cap, large necrotic core, increased macrophages, positive remodeling, and vasa vasorum. Using imaging modalities such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), most of these vulnerable features can be visualized. Of these features, thin fibrous cap is one of the most important determinants of vulnerability.[3−5] It is believed that statins reduce cardiovascular morbidity and mortality through reduction of low-density lipoprotein (LDL) cholesterol. However, pleiotropic effects of statins have also been proposed.[6,7] So far, there has been no head-to-head comparison of plaque stabilization using different statins that result in similar lipid profile changes. The aim of this study was to compare serial changes in plaque characteristics between rosuvastatin and atorvastatin at doses that result in similar levels of lipid reduction.

Methods

In this prospective single-center randomized clinical trial (NCT01023607), 120 patients presenting with *de novo* coronary artery disease undergoing percutaneous coronary intervention and who had ≥1 unstented nonculprit lipid-rich plaque were randomized to rosuvastatin 10 mg daily (R10), atorvastatin 20 mg daily (A20), or atorvastatin 60 mg daily (A60).[8] Patients had clinical assessment, OCT, and IVUS imaging during the index procedure (baseline), 6 months, and 12 months (Figure 1). Nonculprit lipid-rich plaques, defined by OCT as having fibrous cap thickness (FCT) ≤120 μm and lipid arc ≥100°,[9] were evaluated at each timepoint. Comparison of the A20 and A60 groups was previously published, however the R10 group was not included in the previous report.[8]

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See page 1570 for disclosure information.

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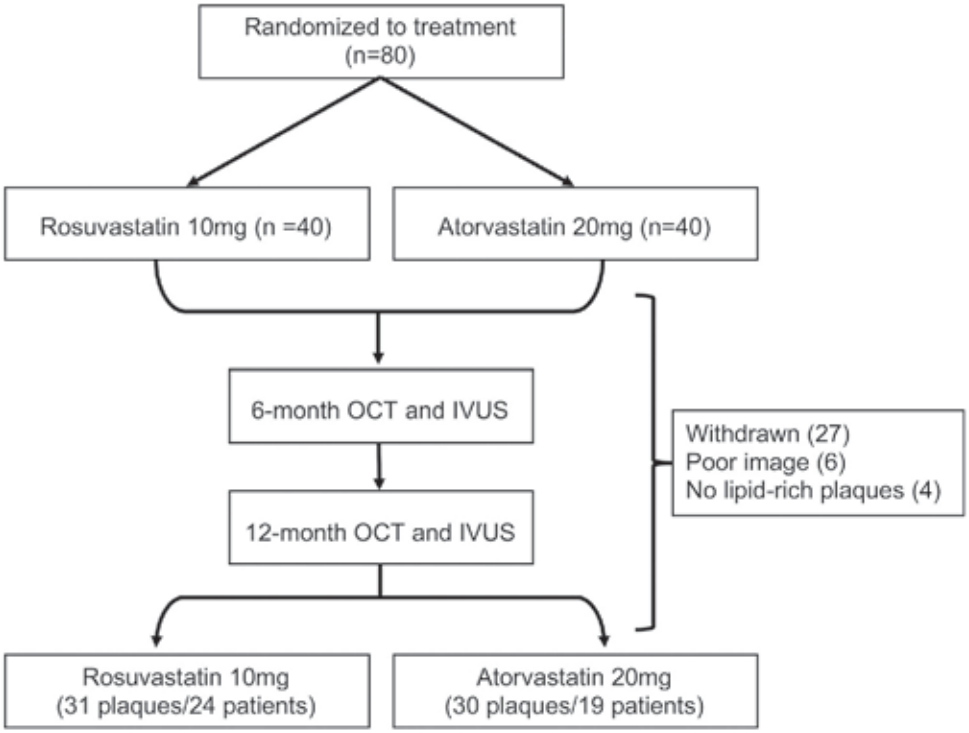


Figure 1. Study design. 80 patients were randomized to rosuvastatin 10 mg or atorvastatin 20 mg daily. Patients had IVUS and OCT imaging at baseline, 6 months, and 12 months. IVUS = intravascular ultrasound; OCT = optical coherence tomography.

Coronary angiography, IVUS, and OCT imaging were performed as previously described.[8] The study protocol was approved by the institutional review board of Harbin Medical Hospital and all patients provided informed consent. All images were independently analyzed by a core laboratory at Massachusetts General Hospital (Boston). Offline quantitative coronary angiography (QCA), OCT, and IVUS analysis were performed by 2 experienced investigators blinded to the patient study group and time point. Minimal lumen diameter, reference vessel diameter, and percent diameter stenosis were measured by QCA (CAAS QCA, Pie Medical Imaging, Maastricht, the Netherlands). OCT images were analyzed at the frame-level in 1 mm intervals and at the lesion-level (Lightlab Imaging, Westford, Massachusetts). Frame-level end points were lipid arc and categorical assessment of microvessels, macrophages, cholesterol crystals, and calcifications.[10–12] Lesion-level endpoints included lipid length, mean lipid arc, and maximum lipid arc. Minimum FCT was measured at the thinnest point 3 times and averaged. Mean lipid index was calculated as the product of the mean lipid arc and lipid length. Lesions were also categorically assessed for thin-cap fibroatheroma (TCFA) morphology. TCFA was defined as a plaque with lipid present in ≥2 quadrants and FCT <65 μm. Baseline and follow-up OCT pullbacks were then matched using fiduciary landmarks (side branches and stent edges) to compare interval changes. Interval changes in each measure were also expressed as the magnitude of the difference and as percent difference.

IVUS analysis was performed offline according to standard guidelines[13] using EchoPlaque (Indec Systems, Mountain View, California). Lumen area and external elastic membrane (EEM) area were analyzed in 1 mm intervals. Plaque area was calculated as EEM area−−lumen area in each image. Plaque burden was calculated as plaque area/EEM area × 100. Total atheroma volume (TAV) was calculated as the sum of all plaque areas per patient. Since pullback length varied between patients, TAV was normalized by the median number of cross sections in the study cohort and expressed as normalized TAV (nTAV). Percent atheroma volume (PAV) was calculated as the sum of all cross-sectional plaque burden values. All interval changes were calculated as follow-up minus baseline.

Outcomes are reported as mean and standard deviation or counts and percentages. Categorical outcomes were evaluated using the chi-square test whereas continuous measures were evaluated using a student's t Test. Comparison of changes in plaque composition and morphology was accomplished through generalized linear modeling using the generalized estimating equations to account for within-patient clustering of multiple plaques over multiple timepoints. All comparisons were 2-sided with an α-level of 0.05 indicating statistical significance. Statistical analysis was performed in MATLAB 2017b (Mathworks, Natick, Massachusetts) with the GEEQ-BOX Statistical Toolbox.[14]

Results

In total, 43 patients (61 plaques) randomized to R10 (24 patients, 31 plaques) or A20 (19 patients, 30 plaques) completed IVUS and OCT imaging at all 3 time points. The mean age was 56.1 years and 63% of patients were male.

Table 1
Baseline characteristics

Variable	R10 (n = 24 patients, 31 plaques)	A20 (n = 19 patients, 30 plaques)	p Value
Age (years)	57.5	54.2	0.22
Men	14 (58%)	13 (68%)	0.72
Hypertension	18 (75%)	12 (63%)	0.61
Dyslipidemia	6 (25%)	5 (26%)	0.80
Diabetes mellitus	14 (58%)	9 (47%)	0.68
Smoker	10 (42%)	8 (42%)	0.77
Previous MI	4 (17%)	4 (21%)	0.98
Previous CABG	0	0 (0%)	1.00
Clinical presentation			
Stable angina pectoris	0	3 (16%)	0.18
Unstable angina pectoris	2 (8%)	1 (5%)	
Non-ST-elevation myocardial infarction	18 (75%)	10 (53%)	
ST-elevation myocardial infarction	4 (17%)	5 (26%)	
Medications			
ACE-I/ARB	11 (46%)	7 (37%)	0.55
Beta-blocker	13 (54%)	11 (58%)	0.81
Calcium channel blocker	8 (33%)	4 (21%)	0.37
Nitrates	15 (63%)	11 (58%)	0.76
Aspirin	24 (100%)	19 (100%)	1.00
Clopidogrel	24 (100%)	19 (100%)	1.00

Dyslipidemia was defined as low-density lipoprotein cholesterol >140 mg/dl.

There were no statistically significant differences in the baseline clinical characteristics of the 2 groups (Table 1). Lumen dimensions did not significantly differ between the groups at any timepoint, nor did they change within each group over the study period (Supplemental Table 1).

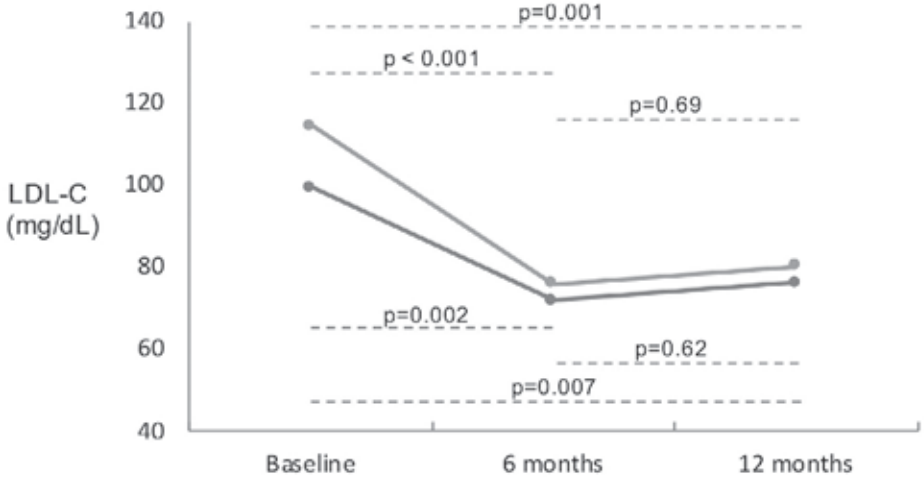
Baseline LDL cholesterol was significantly lower in the R10 group, but otherwise there were no significant differences between the R10 and A20 groups in any other lipid measure or timepoint (Table 2). In both groups, total cholesterol and LDL cholesterol significantly decreased between baseline and 6 months, but did not significantly change between 6 and 12 months (Figure 2). High-density lipoprotein did not change significantly during the study period, and there was no difference between the treatment groups at any time point.

From baseline to 6 months to 12 months, minimum FCT consistently and significantly increased in both groups (Figure 3, Table 3). Between baseline and 6 months, the R10 group had a significantly greater increase in FCT in terms of magnitude and percent (Supplemental Tables 2 and 3). Although both groups continued to show increases in FCT between 6 and 12 months, the R10 group had a higher magnitude and percent increase in FCT (Table 3). Overall, whereas FCT doubled by 12 months in the A20 group, it doubled by 6 months and tripled by 12 months in the R10 group.

Mean lipid arc, maximum lipid arc, and mean lipid index significantly decreased in both groups, but there were no significant differences between the treatment groups (Table 3). These observations were maintained upon considering the magnitude and percent changes in each measure (Supplemental Tables 2 and 3). Neither lipid length nor magnitude of change in lipid length changed significantly in either group, but the percent change was significant in each group between baseline and 12 months.

Table 2
Lipid profile at each time point

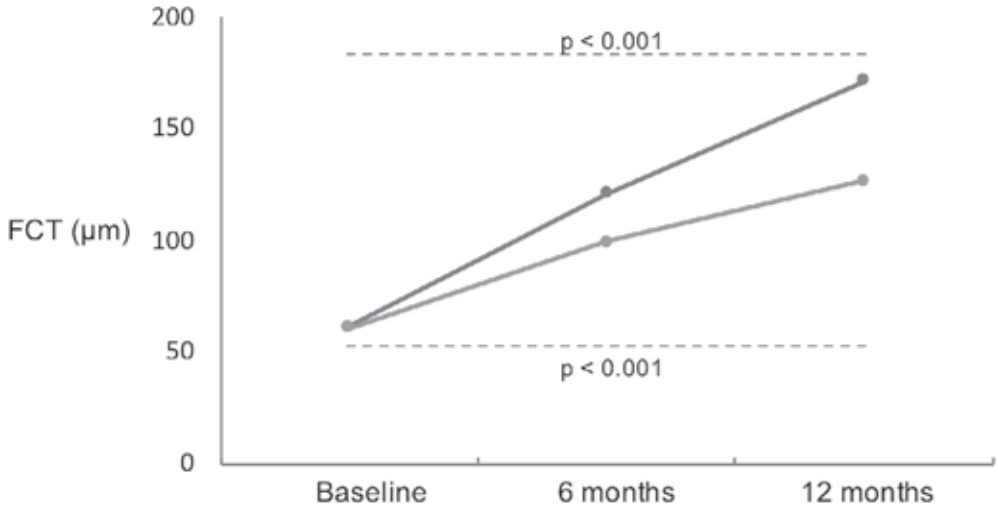
Variable	Time point	R10	A20	p Value
Total cholesterol (mg/dl)	*Baseline*	190 ± 44	203 ± 40	0.35
	6 months	148 ± 39	144 ± 35	0.70
	12 months	154 ± 45	153 ± 49	0.93
	$p\ value_{0\ to\ 6\ months}$	<0.001	<0.001	
	$p\ value_{6\ to\ 12\ months}$	0.63	0.50	
	$p\ value_{0\ to\ 12\ months}$	0.002	<0.001	
Triglycerides (mg/dl)	*Baseline*	245 ± 214	183 ± 83	0.24
	6 months	168 ± 122	135 ± 67	0.30
	12 months	158 ± 70	124 ± 59	0.10
	$p\ value_{0\ to\ 6\ months}$	0.06	0.08	
	$p\ value_{6\ to\ 12\ months}$	0.82	0.64	
	$p\ value_{0\ to\ 12\ months}$	0.05	0.04	
LDL Cholesterol (mg/dl)	*Baseline*	100 ± 21	115 ± 28	0.05
	6 months	72 ± 29	76 ± 28	0.64
	12 months	76 ± 34	80 ± 32	0.70
	$p\ value_{0\ to\ 6\ months}$	0.002	<0.001	
	$p\ value_{6\ to\ 12\ months}$	0.62	0.69	
	$p\ value_{0\ to\ 12\ months}$	0.007	0.001	
HDL Cholesterol (mg/dl)	*Baseline*	51 ± 15	50 ± 12	0.83
	6 months	54 ± 15	49 ± 14	0.26
	12 months	52 ± 13	50 ± 18	0.69
	$p\ value_{0\ to\ 6\ months}$	0.29	0.48	
	$p\ value_{6\ to\ 12\ months}$	0.65	0.79	
	$p\ value_{0\ to\ 12\ months}$	0.62	0.65	



	Baseline	6 months	12 months
Rosuvastatin 10mg	99.58 ± 20.99	71.69 ± 29.11	76.21 ± 33.46
Atorvastatin 20mg	114.73 ± 27.94	75.80 ± 27.71	80.13 ± 32.26
p-value	0.048	0.64	0.70

Figure 2. LDL cholesterol at baseline, 6 months, and 12 months. Serum LDL cholesterol decreased significantly in both groups between baseline and 6 months, however there was no significant change between 6 and 12 months. LDL cholesterol levels were similar between the 2 groups at 6 and 12 months.

The prevalence of TCFA significantly decreased in both the R10 and A20 groups (Table 4). However, between baseline and 12 months, only the R10 group demonstrated a significant decrease in the prevalence of macrophages and microvessels. In contrast, the A20 group showed no significant reduction in either macrophages or microvessels (Table 4). The prevalence of cholesterol crystals or calcifications did not significantly decrease in either group.



	Baseline	6 months	12 months
Rosuvastatin 10mg	61.35 ± 15.88	120.87 ± 57.89	171.52 ± 67.76
Atorvastatin 20mg	60.80 ± 18.09	99.23 ± 47.68	127.03 ± 66.84
p-value	0.90	0.12	0.012

Figure 3. Minimum fibrous cap thickness at baseline, 6 months, and 12 months. While both treatment groups demonstrated significant increases in minimum FCT, the rosuvastatin group showed significantly greater FCT than the atorvastatin group considering all time points (p = 0.03). Further analysis showed that this difference was significant specifically at 12 months (p = 0.012). FCT = fibrous cap thickness.

Table 3
OCT fibrous cap thickness and lipid content at each time point

Variable	Time point	R10	A20	p Value
FCT (μm)	*Baseline*	61.4 ± 15.9	60.8 ± 18.1	0.03
	6 months	120.9 ± 57.9	99.2 ± 47.7	
	12 months	171.5 ± 67.8	127.0 ± 66.8	
	p value	<0.001	<0.001	
Mean lipid arc (°)	*Baseline*	162.4 ± 43.1	174.5 ± 53.8	0.28
	6 months	153.2 ± 48.3	169.5 ± 50.8	
	12 months	141.1 ± 48.4	152.4 ± 62.2	
	p value	<0.001	0.005	
Maximum lipid arc (°)	*Baseline*	235.3 ± 68.4	230.8 ± 72.1	0.79
	6 months	220.9 ± 71.9	229.7 ± 66.9	
	12 months	191.6 ± 70.0	196.2 ± 83.0	
	p value	<0.001	0.003	
Lipid length (mm)	*Baseline*	10.5 ± 4.6	8.1 ± 3.2	0.06
	6 months	10.0 ± 4.6	8.6 ± 3.6	
	12 months	9.8 ± 4.7	7.8 ± 3.5	
	p value	0.08	0.46	
Mean lipid index (°mm)	*Baseline*	1752.8 ± 982.5	1448.6 ± 740.1	0.57
	6 months	1587.8 ± 980.4	1474.4 ± 831.9	
	12 months	1416.9 ± 899.8	1254.9 ± 877.8	
	p value	<0.001	0.005	

FCT = fibrous cap thickness.

In the R10 group, significant decreases were observed for TAV and nTAV, but PAV remained unchanged (Table 5). The A20 group showed no significant changes in TAV, nTAV, or PAV. There were no significant differences in TAV, nTAV, or PAV between the treatment groups at any time point. Furthermore, there was no significant change in the magnitude and percent difference in TAV, nTAV, and PAV over time or between the treatment groups (Supplemental Tables 4 and 5).

Table 4
OCT plaque characteristics at each time point

Variable	Time point	R10	A20	p Value
TCFA	*Baseline*	18 (58%)	21 (70%)	0.25
	6 months	8 (26%)	12 (40%)	
	12 months	3 (10%)	5 (17%)	
	p value	<0.001	<0.001	
Macrophages	*Baseline*	22 (71%)	23 (77%)	0.047
	6 months	19 (61%)	23 (77%)	
	12 months	15 (48%)	23 (77%)	
	p value	0.04	0.76	
Microvessels	*Baseline*	15 (48%)	11 (37%)	0.59
	6 months	10 (32%)	11 (37%)	
	12 months	8 (26%)	9 (30%)	
	p value	0.002	0.23	
Cholesterol crystals	*Baseline*	7 (23%)	7 (23%)	0.40
	6 months	0	0	
	12 months	3 (9.7%)	4 (13%)	
	p value	0.13	0.17	
Calcifications	*Baseline*	14 (45%)	11 (37%)	0.37
	6 months	14 (45%)	11 (37%)	
	12 months	17 (55%)	8 (27%)	
	p value	0.09	0.32	

ns = not significant; TCFA = thin-cap fibroatheroma.

Table 5
IVUS atheroma volume at each time point

Variable	Time point	R10	A20	p Value
TAV (mm^3)	*Baseline*	109.2 ± 62.1	83.3 ± 48.5	0.12
	6 months	101.8 ± 61.1	77.6 ± 43.0	
	12 months	102.5 ± 62.2	77.9 ± 48.6	
	p value	0.047	0.07	
nTAV (mm^3)	*Baseline*	99.0 ± 39.8	89.2 ± 37.7	0.61
	6 months	92.9 ± 40.3	83.8 ± 33.7	
	12 months	92.1 ± 37.2	86.0 ± 33.8	
	p value	0.02	0.20	
PAV (%)	*Baseline*	52.5 ± 9.2	54.5 ± 9.5	0.24
	6 months	52.0 ± 9.1	54.9 ± 9.7	
	12 months	51.3 ± 8.1	54.4 ± 9.5	
	p value	0.13	0.88	

TAV = total atheroma volume; nTAV = normalized total atheroma volume; PAV = percent atheroma volume.

Discussion

In our study, both treatment groups had a similar level of LDL cholesterol reduction, but there was a differential vascular response to each statin in terms of the speed and overall degree of fibrous cap thickening. Although both the R10 and A20 groups had a similar minimum FCT at baseline and similar levels of cholesterol reduction, the R10 group had a more rapid and robust increase that was maintained at 12 months, as evidenced by a nearly 300% average increase from baseline (Figure 4). Essentially, the increase in minimum FCT achieved by the A20 group by 12 months was achieved in 6 months by the R10 group. Furthermore, in both groups, LDL reduction was greatest in the first 6 months and, in fact, did not change further between 6 and 12 months. Yet, in the absence of concomitant LDL reduction, both groups continued to manifest an increase in FCT along with reductions in mean lipid arc, maximum lipid arc, and lipid index. In other words, plaques continued to stabilize in the absence of concurrent LDL reduction. Given that statin-induced plaque changes are more accentuated with higher baseline LDL levels,[15] we hypothesize that the lower baseline LDL level in the R10 group may have led to an underestimation of the differences between the 2 statins.

In addition to lowering LDL cholesterol, in vitro and animal studies suggest pleiotropic effects of statins include vascular endothelial protection,[7,16] antioxidant effects,[6] reduction in coagulation factor activity,[17] and a variety of anti-inflammatory properties.[17–20] Rosuvastatin may also decrease activity of endothelial[21] and monocyte-derived matrix metalloproteinases (MMPs),[22] an effect postulated to reduce fibrous cap thinning, thereby stabilizing atheromatous plaques. Interestingly, we demonstrated a significant decrease in the prevalence of macrophages in the R10 group only. This may be related to decreases in monocyte activation associated with rosuvastatin.[18] We, therefore, postulate that rosuvastatin-induced inhibition of MMPs and monocytic inflammation may play a role in our findings.

In contrast with previous IVUS findings, in our study only the R10 group had a significant reduction in TAV and nTAV, but the percent change in any of the atheroma volume measures was not significant in either group. Patients

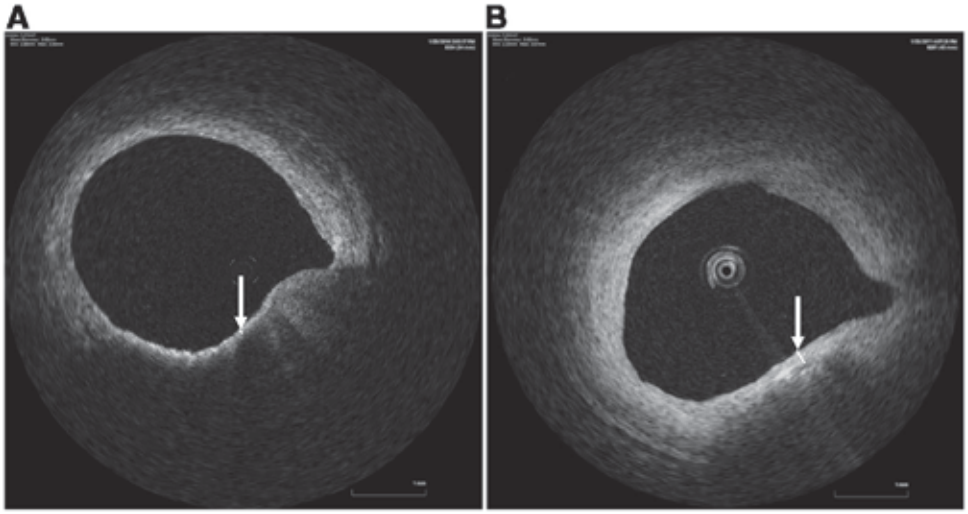


Figure 4. Interval increase in fibrous cap thickness. (*A*) Baseline OCT imaging, minimum FCT is approximately 50 μm (*white arrow*). (*B*) 12-month OCT imaging, minimum FCT has increased to approximately 300μm (*white arrow*). This patient was randomized to rosuvastatin. FCT = fibrous cap thickness; OCT = optical coherence tomography.

with ACS have shown substantially higher percent change in plaque volume: −16.9% and −18.1% in pitavastatin- and atorvastatin-treated patients, respectively, at 8 to 12 months in JAPAN-ACS, and −13.1% at 6 months in the atorvastatin group of ESTABLISH.[23,24] Larger trials in a broader group of patients, however, demonstrated more modest changes. In REVERSAL, at 18 months, the percent change in TAV was +2.7% in the pravastatin group and −0.4% in the atorvastatin group.[25] In SATURN, at 2 years, the change in PAV was −0.99% in the atorvastatin group and −1.22% in the rosuvastatin group.[26] Our results may be explained by use of relatively low statin doses, shorter treatment interval than REVERSAL and SATURN, inclusion of non-ACS patients, and a smaller study cohort, and therefore should not be interpreted as refuting previous studies.

There are several limitations of this study. First, the study cohort was small, primarily due to the invasive nature of serial imaging and related patient attrition. However, imaging at 3 timepoints provided a more comprehensive picture of vascular response to statin therapy over time. Second, this was a single center study performed in an Asian cohort, therefore the results may be less applicable to other populations. Third, we originally designed a 3-arm study investigating 3 groups: rosuvastatin 10 mg, atorvastatin 20 mg, and atorvastatin 60 mg daily. In the previous publication,[8] only analysis of the 2 atorvastatin groups was reported due to the sheer number and complexity of the results. The current work sought to investigate differences in plaque features in the setting of 2 different statins that resulted in similar lipid reduction, providing insight into potential nonlipid mediated effects of statin therapy. Fourth, although there were no significant differences in patients' clinical presentation, only the A20 group had patients presenting with stable angina. Theoretically, this could have played a role in the less-brisk vascular response to atorvastatin therapy. Finally, although we assume that faster and more significant fibrous cap thickening in the rosuvastatin group is morphologically beneficial in terms of plaque stabilization, we do not know if these differences persist beyond 12 months, or whether such differences translate to clinical outcomes.

In conclusion, patients treated with atorvastatin 20 mg or rosuvastatin 10 mg daily showed plaque stabilization even in the absence of continued LDL cholesterol reduction between 6 and 12 months, suggesting nonlipid mediated effects of statin therapy or that vascular structural changes require a sustained low LDL level. Further, despite similar lipid reduction in both groups, the rosuvastatin group had significantly faster and greater increase in FCT, and only the rosuvastatin group demonstrated a significant reduction in prevalence of macrophage density and microvessels as well as TAV. Our results suggest that rosuvastatin has more rapid and potent effects on plaque stabilization and that not all statins have similar effects on plaque stabilization. Whether these observations translate to clinical benefit, warrant larger scale studies with longer term follow-up.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.02.019.

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