Rosuvastatin: Just Another Statin?

A Bandari, M Davidson

Citation

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Abstract

Convincing evidence exists supporting the major role HMG Co-A reductase inhibitors (statins) play in both primary and secondary prevention of cardiovascular diseases given, among other effects, their essential role in the reduction of LDL-C cholesterol . Recently revised guidelines recommend even more intense management of LDL-C cholesterol especially in moderate and high risk patients. Rosuvastatin, the newest statin, offers the most beneficial effects on the lipid profile and particularly, LDL-C. Its safety profile, both pre-approval and post-approval, at the current FDA-doses of 5-40mg is similar to other available statins. Thus, rosuvastatin is an extremely helpful addition to the lipid armamentarium when prescribed at the current FDA approved doses.

INTRODUCTION

The benefits of the 3-hydroxy -3-methylglutaryl coenzyme A reductase inhibitors (statins) for both primary and secondary prevention of cardiovascular disease have been clearly elucidated over the past decade in numerous trials beginning with 4S and culminating in the recently published PROVE-IT trial ([1,2,3,4,5,6,7,8]). The evidence supporting the use of statins has been so convincing that these compounds are now the most prescribed compounds on the market. Still, many patients on statin therapy are unable to reach NCEP ATP III goals and others who may benefit are not on therapy altogether ([9,10]). Furthermore, based on the most up to date evidence, recently published revisions in NCEP ATP III have been formulated ([11]). The updated guidelines, among other suggestions, recommend that in very high risk patients, a goal LDL of <70mg/dl is optimal. Thus, while many patients were not at goal previously, the new guidelines will further reduce the percentage of patients at their LDL goal.

Figure 1

Table 1: Updated Guidelines from the NCEP ATP III Panel

• In high-risk persons, the recommended LDL-C goal is <100 mg/dL. – An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk. – If LDL-C is ≥100 mg/dL, an LDL-lowering drug is indicated simultaneously with lifestyle changes. – If baseline LDL-C is <100 mg/dL, institution of an LDL-lowering drug to achieve an LDL-C level <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence. – If a high-risk person has high triglycerides or low HDL-C, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. – When triglycerides are ≥200 mg/dL, non-HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal.
• For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; – An LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence. – When LDL-C level is 100 to 129 mg/dL, at baseline or on lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL-C level <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence.
• When LDL-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL-C levels.

THE OPTIONS

As of today, six different statins are approved by the FDA for patient use: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Rosuvastatin is the most recently approved of the statins and was introduced in August 2003. Since its introduction, this agent has heralded both great optimism and controversy. Rosuvastatin demonstrates the most pronounced dose-related reductions in LDL cholesterol of any available statin ([12,13,14]). Moreover, it has a highly favorable effect on HDL cholesterol values when compared to other statins ([12]). Still, the 100 deaths resulting from the use of cerivastatin and its subsequent withdrawal from the market has led to a fair amount of

reluctance by the medical community to accept any new statins.

Figure 2

Figure 1

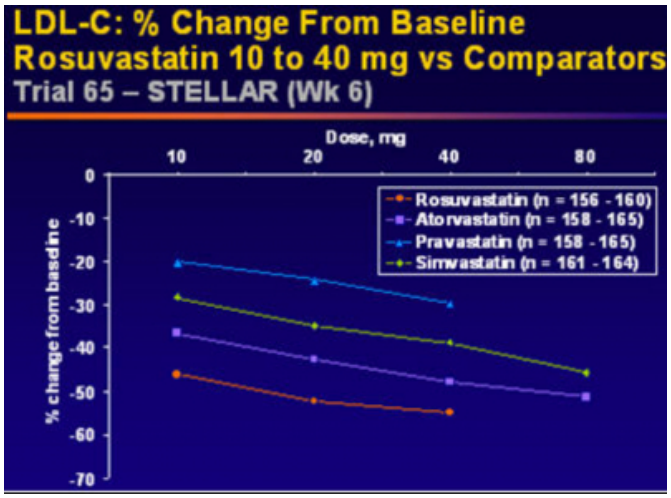
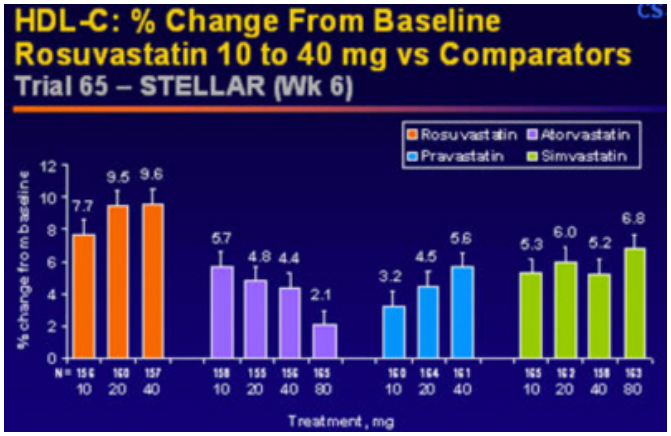


Figure 3

Figure 2

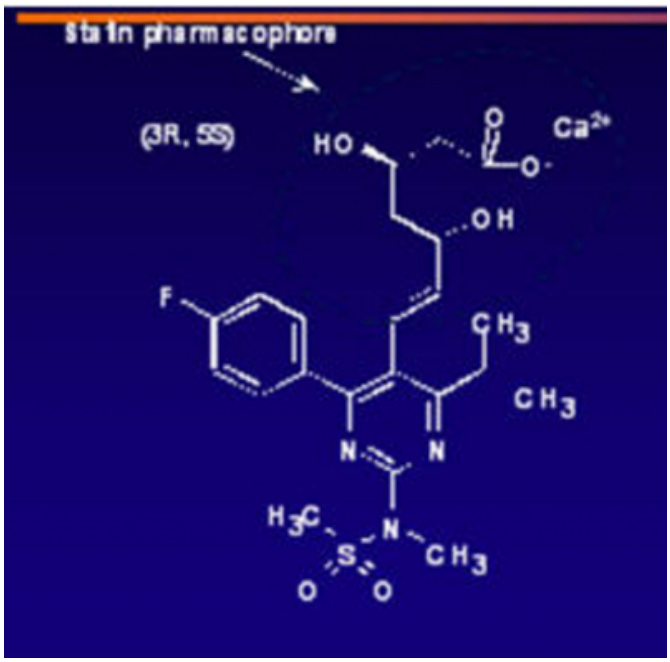


ROSUVASTATIN: IS IT SUPERIOR TO OTHER STATINS?

Rosuvastatin , a synthetic statin, acts as an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase), the principle enzyme involved in the rate-limiting step in cholesterol biosynthesis. Its half-life is roughly 19 hours, longer than any other statin on the market ([15]). Unlike many other statins, rosuvastatin has minimal affect on cytochrome P450. Thus, it has a much lower risk of interactions with many other commonly used pharmacological agents ([16]).

Figure 6

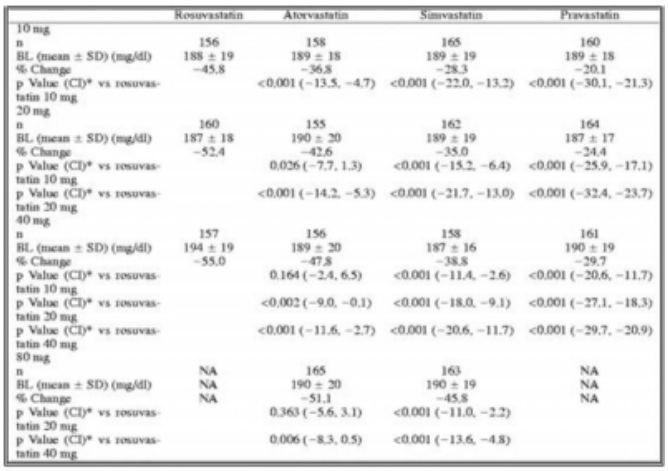
Table 3: Efficacy of Statin Therapy on HDL Cholesterol/Trig. in the STELLAR Trial



Rosuvastatin's effects on the entire lipid profile and particularly LDL-C are superior to any other statin on the market ([12,13,14]). In the STELLAR (Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin) Trial, 2431 hypercholesterolemic adults (LDL-C > 160 mg/dl and < 250 mg/dl; Triglycerides <400 mg/dl) were randomized to treatment with rosuvastatin 10, 20, 40, or 80 mg; atorvastatin 10, 20, 40 or 80mg; simvastatin 10, 20, 40, or 80mg, or pravastatin 10, 20, or 40 mg. Serum lipid compositions were then taken after 6 weeks of therapy. Across dose analysis, it was demonstrated that rosuvastatin 10-40 reduced LDL-C by a mean of 8.2% more than atorvastatin 10-40 mg, 26% more than pravastatin 10 to 40 mg, and 12-18% more than simvastatin 10-80mg (all with P<.001)(12). This data reiterated previously published dose to dose comparisons.

Figure 5

Table 2: Statin Efficacy on LDL-C Cholesterol in the STELLAR Trial



	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin
10 mg				
n	156	158	165	160
BL (mean ± SD) (mg/dl)	188 ± 19	189 ± 18	189 ± 19	189 ± 18
% Change	−45.8	−36.8	−28.3	−20.1
p Value (CI)* vs rosuvastatin 10 mg		<0.001 (−13.5, −4.7)	<0.001 (−22.0, −13.2)	<0.001 (−30.1, −21.3)
20 mg				
n	160	155	162	164
BL (mean ± SD) (mg/dl)	187 ± 18	190 ± 20	189 ± 19	187 ± 17
% Change	−52.4	−42.6	−35.0	−24.4
p Value (CI)* vs rosuvastatin 10 mg		0.026 (−7.7, 1.3)	<0.001 (−15.2, −6.4)	<0.001 (−25.9, −17.1)
p Value (CI)* vs rosuvastatin 20 mg		<0.001 (−14.2, −5.3)	<0.001 (−21.7, −13.0)	<0.001 (−32.4, −23.7)
40 mg				
n	157	156	158	161
BL (mean ± SD) (mg/dl)	194 ± 19	189 ± 20	187 ± 16	190 ± 19
% Change	−55.0	−47.8	−38.8	−29.7
p Value (CI)* vs rosuvastatin 10 mg		0.164 (−2.4, 6.5)	<0.001 (−11.4, −2.6)	<0.001 (−20.6, −11.7)
p Value (CI)* vs rosuvastatin 20 mg		<0.002 (−9.0, −0.1)	<0.001 (−18.0, −9.1)	<0.001 (−27.1, −18.3)
p Value (CI)* vs rosuvastatin 40 mg		<0.001 (−11.6, −2.7)	<0.001 (−20.6, −11.7)	<0.001 (−29.7, −20.9)
80 mg				
n	NA	165	163	NA
BL (mean ± SD) (mg/dl)	NA	190 ± 20	190 ± 19	NA
% Change	NA	−51.1	−45.8	NA
p Value (CI)* vs rosuvastatin 20 mg		0.363 (−5.6, 3.1)	<0.001 (−11.0, −2.2)	
p Value (CI)* vs rosuvastatin 40 mg		0.006 (−8.3, 0.5)	<0.001 (−13.6, −4.8)	

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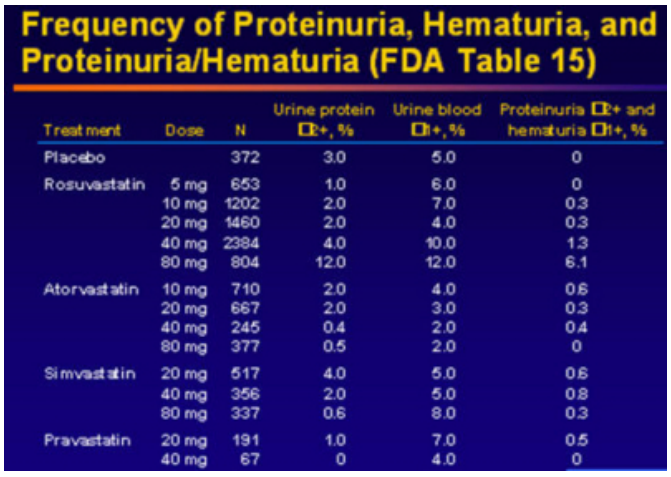
Rosuvastatin also offers superior effects on HDL cholesterol compared to others in its class. At 6 weeks of therapy in the STELLAR trial, rosuvatatin 10 to 40 mg demonstrated a +7.7% to +9.6% increase in HDL compared to a +2.1% to +6.8% increase with atorvastatin, pravastatin, and simvastatin at various doses. Furthermore, unlike atorvastatin, rosuvastatin displayed more pronounced increases in HDL with dose titration upwards. In addition, rosuvastatin faired better than all the statins studied with respect to total cholesterol and triglyceride reductions in this study. Most importanty, in STELLAR, more rosuvastatin patients reached NCEP ATP III and European LDL cholesterol goals than any of the other therapies ([12]).

Figure 8

Figure 4



Frequency of Proteinuria, Hematuria, and Proteinuria/Hematuria (FDA Table 15)

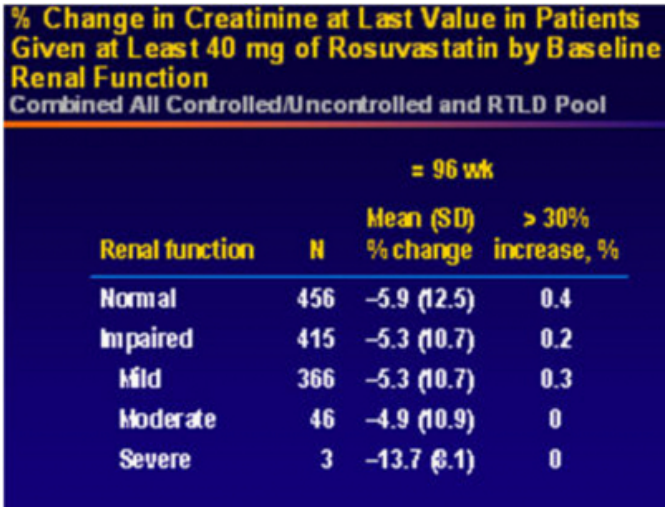
Treatment	Dose	N	Urine protein ☐+, %	Urine blood ☐+, %	Proteinuria ☐+ and hematuria ☐+, %
Placebo		372	3.0	5.0	0
Rosuvastatin	5 mg	653	1.0	6.0	0
	10 mg	1202	2.0	7.0	0.3
	20 mg	1460	2.0	4.0	0.3
	40 mg	2384	4.0	10.0	1.3
	80 mg	804	12.0	12.0	6.1
Atorvastatin	10 mg	710	2.0	4.0	0.6
	20 mg	667	2.0	3.0	0.3
	40 mg	245	0.4	2.0	0.4
	80 mg	377	0.5	2.0	0
Simvastatin	20 mg	517	4.0	5.0	0.6
	40 mg	356	2.0	5.0	0.8
	80 mg	337	0.6	8.0	0.3
Pravastatin	20 mg	191	1.0	7.0	0.5
	40 mg	67	0	4.0	0

STATIN SAFETY: THE LESSON'S-LEARNED FROM CERIVASTATIN

While as a class, the FDA approved statins have been well tolerated with very few adverse events, cerivastatin is the exception and many lessons can be learned from its approval and subsequent discontinuation. Cerivastatin .4mg was approved in the US in May 1999 and cerivastatin .8mg was approved thirteen months later. Of all the statins, cerivastatin was unique given its extremely high potency and bioavailability. Its pre-approval myopathy rates were double the highest previously approved rate but given the safety of other statins, these rates were overlooked ([17]). Moreover, reports were beginning to surface regarding its life-threatening reactions with gemfibrozil which led to warnings on the coadministration included in package labels. Mainly, gemfibrozil as a CYP 2C8 inhibitor ([18]) and inhibitor of statin glucuronidation, causes marked increases in cerivastatin blood levels ([19]). Such coadministration leads to a 20 to 80 fold increase in the rate of rhabdomyolysis and ultimately led to over 100 deaths despite warnings by the manufacturer against using the drugs in combination ([20]). Cerivastatin was removed from the market in August of 2001

Figure 9

Figure 5



% Change in Creatinine at Last Value in Patients Given at Least 40 mg of Rosuvastatin by Baseline Renal Function

Combined All Controlled/Uncontrolled and RTLD Pool

= 96 wk

Renal function	N	Mean (SD) % change	> 30% increase, %
Normal	456	−5.9 (12.5)	0.4
Impaired	415	−5.3 (10.7)	0.2
Mild	366	−5.3 (10.7)	0.3
Moderate	46	−4.9 (10.9)	0
Severe	3	−13.7 (8.1)	0

ROSUVASTATIN SAFETY AFTER CERIVASTATIN

Given the heightened sensitivity to the adverse events of statins in the post-cerivastatin era, the approval of rosuvastatin by the FDA involved much more scrutiny than any previous approval of a statin. This necessitated the pre-approval database to include considerably more patients than any previously approved statin. Doses of 5mg to 80mg were evaluated. The myopathy rates in the 5mg to 40mg

populations ranged from .1%-.2% of the over 16,000 patients evaluated. For the 80mg dose, the incidence of rhabdomyolysis was .4% which prompted the makers of rosuvastatin to discontinue the development of this dose for clinical use. No cases of rhabdomyolysis were observed at any of the other doses($_{21}$).

In addition to rhabdomyolysis, 12% of patients taking 80mg of rosuvastatin developed an increase of > 2+ urine dipstick proteinuria, a finding not previously seen with statin therapy (21). These findings were transient and not associated with a compromise in observed renal function. In the Stellar trial, two female participants developed acute renal failure although confounding variables were present in both cases (12). These latter events led to a delay in approval of rosuvastatin but ultimately, the FDA approved the drug at doses of 5 to 40 mg.

Figure 10

Table 5: Clinically relevant statin drug interactions.

Drug	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin	Rosuvastatin
Azole antifungals	+	-	+	-	+	-
CCBs	-	-	+	-	+	-
Cyclosporine	+	-	+	+	+	+
Erythromycin	+	-	+	-	+	-
Gemfibrozil	NA	-	+	+	+	+
Fenofibrate	NA	NA	NA	-	-	-
HIV PIs	+	-	+	-	+	-
Niacin	-	-	+	-	-	-
Warfarin	+	+	+	+	+	+

+ = Interaction reported; - = No interaction reported.
CCB: Calcium channel blocker (i.e., diltiazem, verapamil); PI: Protease inhibitor

{image:9}

Since its introduction into the market in August 2003, the safety profile of rosuvastatin at the FDA-approved dosing range of 5-40mg is similar to the other statins available today. Even with such a profile, rosuvastatin has still received negative press in relation to its safety profile both in the medical and lay press. In Lancet, an editorial was published highly criticizing Astra Zeneca for marketing rosuvastatin without sufficient outcomes data on its safety ($_{22}$). This criticism failed to account for the significantly larger pre-approval data base (by up to 5 fold) of rosuvastatin compared to other statins.

Earlier this year, a consumer's public health watch dog group strongly petitioned the FDA to withdraw its approval of rosuvastatin. The group, Public Citizen, included several cases of rhabdomyolysis as reasons for its protest ($_{23}$). In particular, the group cited a case of a 39 year old woman who developed rhabdomyolysis on rosuvastatin. After careful analysis, however, it was determined that the etiology of the woman's rhabdomyolysis was an acute myocardial infarction. Rhabdomyolysis is a rare but well-documented adverse event of all statins and its incidence with rosuvastatin therapy at 5mg-40mg is comparible to the incidence with other approved statins according to the FDA Adverse Event Report database ($_{24}$).

ROSUVASTATIN DOSING/INTERACTIONS

The currently recommended starting dose of rosuvastatin is 10 mg dose with titration to 20 mg only if necessary. Caution is advised when increasing the dose to 40mg. It is a class-wide phenomenon that increasing the dose of a statin results in a multiple-fold higher risk of developing myopathy. Thus, this recommendation exists across all statins and not just rosuvastatin. Furthermore, the incidence of myopathy is no higher with rosuvastatin than with other statins at the same dose and not one case of rhabdomyolysis was witnessed in over 16,000 patients taking rosuvastatin in the pre-approval data-base at the 5-40 mg doses (21).

{image:10}

While rosuvastatin is only minimally involved with the cytochrome P450 pathway and drug-drug interactions are few, extreme caution should be exercised with co-adminstration of rosuvastatin with warfarin, cyclosporine, and gemfibrozil. Rosuvastatin may cause a more pronounced increase in INR for patients on warfarin and thus, close monitoring of patients should be exercised when rosuvastatin is initially prescribed for patients taking warfarin. This caution should also be applied when doses are titrated until a fairly steady INR and warfarin dose is achieved ($_{25}$).

Cyclosporine increases the dose of all statins including rosuvastatin by several fold. Thus, the only recommeded dose of rosuvastatin for patients on cyclosporine should be 5 mg. In patients with severe renal impairment, similar dosing modifications should be followed given that in such patients, rosuvastatin is partially renally excreted. Doses should not exceed 10 mg in these patients($_{25}$).

As with other statins, gemfibrozil does raise serum rosuvastatin concentrations ($_{17}$). For patients taking gemfibrozil 600 mg bid, the Cmax and AUC of rosuvastatin increases by 2.2 and 1.9 fold respectively ($_{23}$). Thus, we do not recommend the use of rosuvastatin and gemfibrozil together especially given the cerivastatin outcomes. If combination therapy is deemed necessary to achieve NCEP ATP III goals, the use of ezetimibe, fenofibrate, or colesevelam is a safer alternative depending on the clinical scenario. If gemfibrozil is to be used in combination with

rosuvastatin, the manufacturer suggests that only the 5mg and 10mg doses are prescribed ([25]).

With the recently released guidelines recommending more intense reductions in LDL cholesterol levels, rosuvastatin should be seriously considered as the primary choice of therapy in high risk patients and those unable to reach their recommended LDL goals. In addition, given the fact that rosuvastatin has minimal interaction with the cytochrome P450 system, it also provides the added benefit of fewer drug to drug interactions than most other statins. Still, outcome data with rosuvastatin is not yet available given its relatively short time on the market with respect to other statins. Such data is currently being compiled. That withstanding, given the superiority of rosuvastatin in the modification of the entire lipid profile when compared to all other statins and its equivalent safety profile to other statins, rosuvastatin is an extremely helpful addition to the lipid armamentarium when prescribed at the current FDA approved doses.

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Author Information

Armin Bandari, M.D.
Department of Internal Medicine, Rush University Medical Center

Michael H. Davidson, M.D.
Director, Rush University Medical Center