National PBM-MAP Drug Monograph
Rosuvastatin (Crestor®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and The Medical Advisory Panel

Executive Summary

Efficacy

- In 6 randomized, head-to-head statin comparative clinical trials, 10 mg of rosuvastatin resulted in a reduction in LDL-C of between 43-49%. The approximate equivalent daily dose of simvastatin and atorvastatin to rosuvastatin 10 mg are 80 mg and 40 mg, respectively.
- With regard to HDL-C elevation and triglyceride lowering, rosuvastatin produced changes similar to that seen with the other statins, with few exceptions.
- There are currently no published clinical trials demonstrating a reduction in health outcomes with rosuvastatin.

Safety

- In pre-marketing controlled clinical trials, over 10,000 patients have been exposed to rosuvastatin. The most common adverse events included myalgia, constipation, asthenia, abdominal pain and nausea and were similar to those seen with other statins.
- Clinically significant elevation in liver function tests (LFTs, >3X upper limit of normal) was reported in 0-0.4% of patients receiving doses up to 40 mg daily.
- Clinically significant elevation in creatine kinase (CK, >10X upper limit of normal) was reported in 0.2-0.4% of patients taking up to 40 mg daily.
- Symptomatic myopathy, with significant elevation in CK, was reported in 0.1% of patients taking up to 40 mg of rosuvastatin daily.
- In the rosuvastatin clinical trials program, one case of rhabdomyolysis was reported with the 10 mg dose and 7 cases with the 80 mg dose. Rhabdomyolysis was not observed in pre-marketing clinical trials of other available statins.
- In the Stellar trial, 2 patients on rosuvastatin 80 mg per day developed renal failure of unknown etiology with one requiring short-term hemodialysis.
- Myopathy, not related to exercise or injury, was seen in 11 patients on rosuvastatin 80 mg and in 1 patient in each of the 10, 20 and 40 mg doses. No cases of myopathy were reported in the rosuvastatin 5 mg dose group.
- As a result of the higher number of reports of rhabdomyolysis and renal impairment, development of the 80 mg dose was halted.
- Dipstick-positive proteinuria and microscopic hematuria were noted in the rosuvastatin clinical trials program. These laboratory abnormalities occurred primarily in those receiving rosuvastatin at a dose of 80 mg daily but also occurred at a higher rate in those receiving the 40 mg dose compared to those on lower doses of rosuvastatin or comparator statins.
- Although renal function monitoring is not recommended, dose reduction from 40 mg daily is recommended in those patients with unexplained persistent proteinuria during routine urinalysis testing.
- AstraZeneca and the FDA addressed safety concerns with the 40 mg dose by limited distribution plans. This plan requires that the 40 mg dose would not be stocked directly with retail pharmacies but would be available through wholesalers. This will create a one-day lag for the 40 mg dose ensuring that only patients requiring this dose will be able to obtain it.

Precautions/Contraindications

- Precautions and contraindications for rosuvastatin are similar to other statins. Patients receiving statins should always be instructed to report any unexplained muscle tenderness, pain or weakness to their healthcare provider immediately.
- In Japanese and Chinese individuals residing in Japan and Singapore, median exposure to rosuvastatin was increased 2-fold. The manufacturer has agreed to study Asians residing in the United States to further explore the differences in rosuvastatin's pharmacokinetics. As a result,

rosuvastatin should not be administered to Asian veterans until data from these planned studies are available.

- In patients with severe renal impairment (e.g. CL_{cr} <30 mL/min/1.73 m^2), the initial dose of rosuvastatin should be 5 mg daily and the maximum daily dose is not to exceed 10 mg daily. In patients on hemodialysis, the dose of rosuvastatin should be limited to 5 mg daily.

Drug Interactions

- Only about 10% of rosuvastatin is metabolized, primarily via CYP 2C9. It is not metabolized via CYP 3A4 and is therefore not vulnerable to interactions with known CYP 3A4 inhibitors.
- When combined with cyclosporine, the dose of rosuvastatin should not exceed 5 mg daily
- When combined with gemfibrozil, the dose of rosuvastatin should start at 5 mg and not exceed 10 mg daily.
- Upon initiation of rosuvastatin, the International Normalized Ratio (INR) increased significantly (>4, baseline 2-3) in several patients stabilized on warfarin. Excessive anticoagulation has also been reported for other statins (e.g. fluvastatin, lovastatin, pravastatin and simvastatin). Therefore, INR should be monitored before and frequently during early treatment with rosuvastatin in patients on warfarin.
- Antacids can reduce the plasma concentrations of rosuvastatin by 54% when taken within 2 hours of a dose. As a result, antacids should be given 2 or more hours after rosuvastatin.

Dosing

- The usual starting dose of rosuvastatin is 10 mg daily. However, in patients requiring less vigorous LDL-C reduction and those with factors predisposing them to myopathy (e.g. advanced age, renal insufficiency, hypothyroidism, etc.), a starting dose of 5 mg daily is recommended.
- The maximum approved dose is 40 mg daily.
- Please see monograph for dosing in special populations and circumstances.
- Rosuvastatin can be given without regard to meals and at any time during the day.

Laboratory Monitoring

- As with other statins, the manufacturers package insert recommends that patients on rosuvastatin should have their liver function tests measured at baseline and at 12 weeks following both initiation of therapy and dose escalation, and periodically thereafter.

Recommendations

- Since the VA has 3 statins on the National Formulary and the long-term safety (>1 year) of rosuvastatin is unknown, it is recommended that rosuvastatin not be added to the National or VISN formularies.
- However, it can be considered on a nonformulary basis for those patients receiving potent CYP 3A4 inhibitors who are unable to meet ATP III LDL-C goals on fluvastatin or pravastatin (nonformulary). http://vapbm.org/criteria/Fluva-prava-atorva-r.pdf A starting dose of 5 mg daily is recommended in these individuals.
- It can also be considered in those patients not meeting their LDL-C goals on maximally tolerated doses of other available statins with longer safety records (e.g. lovastatin or simvastatin and then atorvastatin (nonformulary)).
- The VA Medical Advisory Panel (MAP) has recommended 20 mg to be the maximum daily dose of rosuvastatin in the veteran population until more safety data are available for the 40 mg dose. However, 40 mg daily can be considered if a provider deems necessary. In those patients on 40 mg daily, baseline and periodic urinary and renal function monitoring are recommended. If unexplained, persistent proteinuria is noted in a patient receiving rosuvastatin 40 mg daily, the manufacturer recommends reducing the dose of rosuvastatin.
- Finally, rosuvastatin should not be used in Asian individuals until results from the planned pharmacokinetic study of Asians residing in the United States are available.

Methods

Literature Search

MEDLINE [Pubmed-1966-2002] was searched using the terms rosuvastatin and Crestor®.
Reference lists of review articles were searched for relevant clinical trials. In addition, information from reliable sources such as The Pink Sheet, the FDA website and the Medical Letter were included.
The manufacturers of rosuvastatin submitted a package insert and an AMCP dossier.

Eligibility Criteria and Study Selection

All randomized clinical trials in humans, English language, and published in peer-reviewed journals, were included.

Introduction

Coronary heart disease (CHD) continues to be the leading cause of mortality and a significant cause of morbidity among Americans. In 1999, CHD claimed 529,659 lives, translating into about 1 out of every 5 deaths in the United States.[1] Elevated cholesterol, or hypercholesterolemia, is an important risk factor for CHD. The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are an important component of care in the management of hypercholesterolemia because of their effectiveness in reducing low-density lipoprotein (LDL-C), their safety and tolerability, and because of their demonstrated ability to reduce cardiovascular morbidity and mortality in clinical trials. The statins work by blocking the enzyme HMG-CoA reductase. This enzyme assists in the manufacture of cholesterol. Upon blocking HMG-CoA reductase, there is a reduction in cholesterol production. As a result of this reduction, a greater number of LDL receptors are created thereby increasing the uptake of LDL-C. As a result, treatment with statins reduces the amount of cholesterol made by the body. This reduction in cholesterol production results in reduced LDL-C, total cholesterol, and triglycerides and slightly increases high-density lipoprotein (HDL-C).

Rosuvastatin (Crestor®) is the most recent statin to be approved by the Food and Drug Administration (FDA).

Pharmacology/Pharmacokinetics

Rosuvastatin works in the same way as other statins to reduce LDL-C, total cholesterol and triglycerides and to increase HDL-C.

Table 1. Pharmacokinetic Properties[2-7]

Parameter	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Bioavailability	14%	24%	< 5%	17%	20%	< 5%
Mean Half-life (hours)	14-21	<2*	3-4	1.8	19	3
Excretion: Renal Feces	 < 2% 98%	 5% 90%	 10% 83%	 20% 70%	 10% 90%	 13% 60%
Metabolic enzymes	CYP 3A4	CYP 2C9	CYP 3A4	Sulfation	CYP 2C9, 2C19	CYP 3A4
Metabolites contributing to lipid lowering effect	Yes	No	Yes	No	No	Yes
Hepatic first pass effect	20-30%	40-70%	40-70%	50-70%	Unknown	50-80%
Lipophilicity	Lipophilic	Hydrophilic	Lipophilic	Hydrophilic	Hydrophilic	Lipophilic

*Fluvastatin XL t ½ is 3-6 hours depending upon fed or fasted state.

FDA Indications[7]

1. As an adjunct to diet to reduce elevated total cholesterol, LDL-C, ApoB, nonHDL-C, and triglyceride levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb).
2. As an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).
3. To reduce LDL-C, total cholesterol, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Current VA National Formulary Status

Rosuvastatin is currently nonformulary in the VA. Formulary statins include lovastatin and simvastatin. In addition, fluvastatin is available on the formulary for those patients receiving known potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g. macrolide antibiotics, azole antifungals, protease inhibitors, etc.).

Dosage and Administration[7]

The usual starting dose of rosuvastatin is 10 mg daily. However, in patients requiring less vigorous LDL-C reduction and those with factors predisposing them to myopathy (e.g. advanced age, renal insufficiency, hypothyroidism, etc.), a starting dose of 5 mg daily is recommended. The maximum approved dose is 40 mg daily.

Rosuvastatin can be given without regard to meals and at any time during the day.

Table 2. Rosuvastatin Dosing in Special Circumstances

Special Circumstance	Starting Daily Dose	Maximum Daily Dose
Those predisposed to myopathy (advanced age (>70 years), chronic renal impairment, hypothyroidism, receiving multiple medications, etc.)[18, 19]	5 mg	20 mg*
Severe renal impairment (CL_{cr}<30 ml/min/1.73 m^2)	5 mg	10 mg
Hemodialysis Recipients	5 mg	5 mg
Combined with cyclosporine	5 mg	5 mg
Combined with gemfibrozil	5 mg	10 mg
Asians	NR	NR

NR=not recommended until planned pharmacokinetic studies in Asians residing in the US are completed

* The maximum recommended daily dose of rosuvastatin should be 20 mg in the veteran population until more safety data are available for the 40 mg daily dose.

Adverse Effects

In clinical trials involving more than 10,000 patients, 3.7% withdrew from treatment due to adverse effects. The most commonly reported events thought to be related to rosuvastatin treatment included myalgia, constipation, asthenia, abdominal pain, and nausea.

Table 3. Adverse Events in Placebo-Controlled Trials[7]

Adverse Event	Rosuvastatin (n=744)	Placebo (n=382)
Myalgia	2.8 %	1.3%
Diarrhea	3.4%	2.9%
Dyspepsia	3.4%	3.1%
Nausea	3.4%	3.1%
Asthenia	2.7%	2.6%

Study discontinuation due to ADE was reported in 3% of rosuvastatin and 5% of placebo recipients during trials of up to 12 weeks in duration.

In clinical trials, similar to the other available statins, administration of rosuvastatin was associated with clinically significant elevation in liver function tests (>3X upper limit of normal) in 0-0.4% of patients taking 5-40 mg of rosuvastatin daily. In addition, clinically significant elevation in creatine kinase (CK) (>10X upper limit of normal) was reported in 0.2-0.4% of patients taking up to 40 mg daily of rosuvastatin and symptomatic myopathy, with significant elevation in CK, was reported in 0.1% of those taking up to 40 mg daily of rosuvastatin.

In the rosuvastatin clinical trials program, one case of rhabdomyolysis was reported with the 10 mg dose and 7 cases with the 80 mg dose. Myopathy, not related to exercise or injury, was seen in 11 patients on rosuvastatin 80 mg and in 1 patient in each of the 10, 20 and 40 mg doses. No cases of myopathy were reported in the rosuvastatin 5 mg dose group. As a result of the higher number of reports of rhabdomyolysis and renal impairment, development of the 80 mg dose was halted.[8] Rhabdomyolysis was not observed in

pre-marketing clinical trials of other available statins. In the Stellar trial, 2 patients receiving rosuvastatin 80 mg per day developed renal failure of unknown etiology with one requiring short-term hemodialysis.[15]

Dipstick-positive proteinuria and microscopic hematuria were noted in the rosuvastatin clinical trials program. These laboratory abnormalities occurred primarily in those receiving rosuvastatin at a dose of 80 mg daily but also occurred at a higher rate in those receiving the 40 mg dose compared to those on lower doses of rosuvastatin or comparator statins. The manufacturers commented that these laboratory findings were typically transient and not associated with worsening renal function and that the clinical significance is not known. However, dose reduction from 40 mg daily is recommended in those patients with unexplained persistent proteinuria during routine urinalysis testing. Reportedly, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended requiring renal function monitoring in those patients receiving 40 mg daily of rosuvastatin. However, this recommendation was not included in the product information. Instead, it was reported that AstraZeneca and the FDA addressed safety concerns with the 40 mg dose by limited distribution plans. This plan requires that the 40 mg dose would not be stocked directly with retail pharmacies but would be available through wholesalers. The belief is that this would create a one-day lag for the 40 mg dose ensuring that only patients requiring this dose would be able to obtain it.

Table 4. Percentage of Patients with 2+ Dipstick-Positive Urine Protein on Statins[8]

Statin	Dose	Dipstick-Positive Urine Protein >2% (%)
Rosuvastatin	5 mg	0.5%
	10 mg	0.8%
	20 mg	0.5%
	40 mg	2.8%
	80 mg	11%
Atorvastatin	10 mg	0.6%
	20 mg	0.8%
	40 mg	0.4%
	80 mg	0.3%
Pravastatin	20 mg	1.1%
	40 mg	0%
Simvastatin	20 mg	1.1%
	40 mg	0.6%
	80 mg	0.3%

Precautions/Contraindications

Precautions:

As with all statins, patients should be instructed to report any unexplained muscle tenderness, pain or weakness to their healthcare provider immediately. Rosuvastatin should be used with caution in those patients known to consume significant amounts of alcohol or who have a history of liver disease.

In pharmacokinetic studies, conducted in Japanese and Chinese subjects living in Japan and Singapore, there was a 2-fold increase in median exposure to rosuvastatin compared with Caucasians living in the United States. As a result, the manufacturer of rosuvastatin has agreed to conduct a pharmacokinetic study of Asians residing in the United States to further examine the differences in rosuvastatin pharmacokinetics seen in earlier studies. The authors of a recent issue of the Medical Letter recommend that rosuvastatin be reserved for non-Asian individuals not achieving an adequate response to statins with a longer safety record until more data are available.[17]
Administration of rosuvastatin to patients with severe renal impairment resulted in a 3-fold increase in plasma concentrations of rosuvastatin. As a result, candidates for rosuvastatin with severe renal impairment (e.g. CL_{cr} <30 mL/min/1.73 m^2) should receive an initial dose of 5 mg and not exceed 10 mg daily.

Contraindications:

Similar to the other statins, rosuvastatin is contraindicated in patients with known hypersensitivity to any of its components. Also in those patients with active liver disease or with unexplained persistent elevation in

liver transaminases. Rosuvastatin is contraindicated in pregnancy and women of childbearing age should only be considered candidates for rosuvastatin if they are extremely unlikely to conceive.

Laboratory Monitoring

As with other statins, the manufacturers package insert recommends that patients on rosuvastatin should have their liver function tests measured at baseline and at 12 weeks following both initiation of therapy and dose escalation, and periodically thereafter.

Drug Interactions

Rosuvastatin is not extensively metabolized. Approximately 10% of a radiolabeled dose is recovered as metabolites. The primary metabolite, which does not contribute significantly to rosuvastatin's lipid lowering effect, is formed primarily by cytochrome P450 2C9 (CYP 2C9). Rosuvastatin is not metabolized via CYP 3A4 and is therefore not vulnerable to interactions with known CYP 3A4 inhibitors.

When rosuvastatin was combined with cyclosporine, cyclosporine plasma concentrations were not changed. However, the area under the curve (AUC) and Cmax for rosuvastatin were increased 7 and 11-fold, respectively. As a result, the dose of rosuvastatin should be limited to 5 mg daily when combined with cyclosporine.

When rosuvastatin was combined with fenofibrate, there were no changes in the plasma concentrations of either agent. However, when rosuvastatin (80 mg) was combined with gemfibrozil (600 mg bid), rosuvastatin's AUC increased by 90% and Cmax by 120%. When rosuvastatin is combined with gemfibrozil, the dose should be limited to 10 mg daily.

There are currently no published studies demonstrating the effect of niacin on rosuvastatin's plasma concentrations. There is one unblinded, 24 week trial in which 270 patients received either rosuvastatin 40 mg daily, extended release niacin 2 g daily, rosuvastatin 40 mg daily plus extended release niacin 1 g daily or rosuvastatin 10 mg daily plus extended release niacin 2 g daily. In this trial, there were no serious adverse events considered related to study medications. There were no clinically significant increases in liver function tests (LFTs) or creatine kinase (CK) during the trial.[9]

When rosuvastatin was given to patients stabilized on warfarin, clinically significant elevation in their International Normalized Ratio (INR) was observed (>4, baseline 2-3) in several patients. There have also been reports of excessive anticoagulation in patients receiving other statins (lovastatin, simvastatin, fluvastatin and pravastatin) in combination with warfarin. As a result, the INR should be monitored closely when statins are initiated or discontinued in patients stabilized on warfarin. These patients should also be warned to observe for signs of bleeding.[10]

Antacids may reduce the plasma concentrations of rosuvastatin by 54% when taken within 2 hours of a dose. However, when the antacid was given 2 or more hours after rosuvastatin, there was no change in rosuvastatin plasma concentrations.

Clinical Trials

Clinical trials were included that measured:

Intermediate outcome measures:
1. LDL-C, total cholesterol and triglyceride reduction and HDL-C elevation.
2. Percentage of patients meeting NCEP or ATP III goals.

And/Or

Health outcomes:
Cardiac death, nonfatal MI, CHD (angina), coronary revascularization procedures (coronary artery bypass grafting, angioplasty or stent placement), all-cause mortality and stroke.

There are 6 trials examining rosuvastatin's effect on lipoproteins (e.g. LDL-C, HDL-C, TC, triglycerides, etc.) compared to other statins. Five of these trials were blinded and 1 was unblinded. Each trial was similar in design and randomized men or women ≥18 years or older with a LDL-C of >160 mg/dl and <250 mg/dl and a triglyceride level <400 mg/dl. Each patient underwent a dietary lead-in period during which they were instructed to follow a National Cholesterol Education Program (NCEP) step 1 diet and continued this diet throughout the study. Exclusion criteria were typical of other statins studies. Although the trial authors stated that intention to treat statistics were used, patients withdrawing from the study after the first dose or prior to first lipoprotein test were not included in the efficacy analysis.

Table 5. Clinical Trials: Intermediate Health Outcome Measures

Clinical Trial	Intervention	Results	Safety/Comments
Olsson AG 2002 [11] R, DB, MC 12 weeks (fixed dose) 40 weeks (dose titrate) n=412 (AstraZeneca)	Atorva 10 mg qd Rosuva 5 mg qd or Rosuva 10 mg qd AHA Step I diet	% LDL-C Reduction from baseline (12 wks) Atorva: 39 % Rosuva 5 mg: 46% Rosuva 10 mg: 50% (p<0.001 in favor of rosuva 5 and 10 mg) % LDL-C Reduction from baseline (52 wks)-mean dose Atorva 20.8 mg: 44% Rosuva 9.8 mg: 47% Rosuva 13.4 mg: 53% (p<0.05 in favor of rosuva 5 and 10 mg) % TG Reduction from baseline (12 wks) Atorva: 16 % Rosuva 5 mg: 15 % Rosuva 10 mg: 19 % (NS) % HDL-C Increase from baseline (12 wks) Atorva: 6% Rosuva 5 mg: 6% Rosuva 10 mg: 8% (NS) % Reaching ATP III LDL-C Goals (12 wks) Atorva: 71% Rosuva 5 mg: 84% Rosuva 10 mg: 89% (No statistical analysis performed)	Seventeen percent (69) of randomized patients withdrew from treatment. Among the 28 patients withdrawing due to ADE and considered to be related to study meds, 5 occurred in each Rosuva group and 8 in the Atorva group. None of the patients reporting myalgia had clinically significant elevation in CK and no cases of myopathy were reported.
Davidson M. 2002 [12] R, DB, PC, MC 12 weeks (fixed dose) n=519 (AstraZeneca)	Atorva 10 mg qd Rosuva 5 mg qd Atorva 10 mg qd or Placebo AHA Step I Diet	% LDL-C Reduction from baseline (12 wks) Atorva: 35% Rosuva 5 mg: 40% Rosuva 10 mg: 43% Placebo: 0% (p<0.01 in favor of rosuva 5 and 10 mg vs. atorva) % TG Reduction from baseline (12 wks) Atorva: 19% Rosuva 5 mg: 17% Rosuva 10 mg: 19% Placebo: 1% (NS) % HDL-C Increase from baseline (12 wks) Atorva: 8 % Rosuva 5 mg: 13 % Rosuva 10mg: 12 % Placebo: 4% (p<0.05 in favor of Rosuva 5 and 10 mg vs. atorva) % Reaching ATP III LDL-C Goals (12 wks) Atorva: 72% Rosuva 5 mg: 84% Rosuva 10 mg: 82% (No statistical analysis performed)	Thirty-six patients withdrew from the study. Twenty-one due to ADE. Withdrawal due to ADE occurred in 4 (3.1%) atorva, 7 (5.3%) placebo, 6 (4.7%) rosuva 5mg, and 4 (3.1%) rosuva 10 mg patients. No serious ADE were considered related to treatment. No clinically significant elevation in CK or LFTs were seen in any group.

<table>
<tr>
<td>Paoletti R. 2001 [13]
R, DB, MC
12 weeks (fixed dose)
n=602

(AstraZeneca)</td>
<td>Prava 20 mg
Rosuva 5 mg
Rosuva 10 mg or
Simva 20 mg</td>
<td><u>% LDL-C Reduction from baseline (12 wks)</u>
Prava: 28%
Rosuva 5 mg: 42%
Rosuva 10 mg: 49%
Simva: 37%
(p<0.01 in favor of rosuva 5 and 10 mg vs. prava and simva)
<u>% TG Reduction from baseline (12 wks)</u>
Prava: 13%
Rosuva 5 mg: 12%
Rosuva 10 mg: 18%
Simva: 14%
(NS)
<u>% HDL-C Increase from baseline (12 wks)</u>
Prava: 4 %
Rosuva 5 mg: 6 %
Rosuva 10mg: 7 %
Simva: 4%
(NS)
<u>% Reaching ATP III LDL-C Goals (12 wks)</u>
Prava: 46%
Rosuva 5 mg: 64%
Rosuva 10 mg: 84%
Simva: 64%
(No statistical analysis performed)</td>
<td>Twenty-eight patients withdrew from treatment. Twelve due to ADE. ADE leading to withdrawal occurred in 3 (2.2%) prava, 2 (1.6%) rosuva 5 mg, 6 (5.2%) rosuva 10 mg, and 1 (0.8%) of simva patients. No serious ADE occurred in any group but rosuva 10 mg. Four serious ADE occurred in rosuva 10 mg (cerebral hemorrhage, MI, syncope and cholecystitis). All of these events were NOT considered to be related to study medication. No patient experienced clinically significant increases in LFTs or CK.</td>
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<tr>
<td>Brown WV. 2002 [14]
R, DB, MC
12 weeks (fixed dose)
40 weeks (dose titrate)
n=477

(AstraZeneca)</td>
<td>Prava 20 mg
Rosuva 5 mg
Rosuva 10 mg or
Simva 20 mg</td>
<td><u>% LDL-C Reduction from baseline (12 wks)</u>
Prava: 26.5 %
Rosuva 5 mg: 39.1 %
Rosuva 10 mg: 47.4%
Simva: 34.6%
(p<0.001 in favor of rosuva 5 and 10 mg vs. prava and simva)
<u>% LDL-C Reduction from baseline (52 wks)-mean dose</u>
Prava 32.6 mg: 31.6%
Rosuva 9.5 mg: 41.6%
Rosuva 13.8 mg: 48%
Simva 36.3%
(p<0.001 in favor of rosuva 10 mg vs. prava and simva. p<0.001 in favor of rosuva 5 mg vs. prava only)
<u>% TG Reduction from baseline (12 wks)</u>
Prava: 11.4 %
Rosuva 5 mg: 17.6 %
Rosuva 10 mg: 21.5 %
Simva: 10.2%
(p<0.05 in favor of rosuva 5 mg vs. simva, p<0.001 in favor of rosuva 10 vs. prava and simva)
<u>% HDL-C Increase from baseline (12 wks)</u>
Prava: 8.3%
Rosuva 5 mg: 8.2%
Rosuva 10 mg: 11.9%
Simva: 8.8%
(p<0.05 in favor of rosuva 10 mg vs. prava only)
<u>% Reaching ATP III LDL-C Goals (52 wks)-mean dose</u>
Prava 32.6 mg: 50.9%
Rosuva 9.5 mg: 77.7%
Rosuva 13.8 mg: 87.8%
Simva: 36.3 mg %
(No statistical analysis performed)</td>
<td>Authors noted that some patients were not titrated to their max. statin dose despite not meeting ATP II goals. Also, max dose of prava at the time of the study was only 40 mg/day.

Twenty-eight percent (n=81) of patients did not complete the trial. Forty-two withdrew due to ADE. Of those, 27 were considered related to study medications. No differences were noted between groups.

Mean compliance between all groups was low at 62% for both rosuva groups, 69% for prava and 68% for simva over 52 weeks.</td>
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<tr>
<td>Jones PH. 2003 [15]
R, OL, MC
6 weeks (fixed dose)
n=2,341

(AstraZeneca)</td>
<td>Atorva 10,20,40,80
Prava 10, 20, 40
Rosuva 10,20,40,80
Simva 10,20,40,80</td>
<td><u>% LDL-C Reduction from baseline (6 wks)</u>
<table>
<tr><th></th><th>10 mg</th><th>20 mg</th><th>40 mg</th><th>80 mg</th></tr>
<tr><td>Atorva</td><td>36.8</td><td>42.6</td><td>47.8</td><td>51.1</td></tr>
<tr><td>Prava</td><td>20.1</td><td>24.4</td><td>29.7</td><td>--</td></tr>
<tr><td>Rosuva</td><td>45.8</td><td>52.4</td><td>55</td><td>NR</td></tr>
<tr><td>Simva</td><td>28.3</td><td>35</td><td>38.8</td><td>45.8</td></tr>
</table>
-Rosuva 10 statistically better than: Atorva 10 and 20 mg, all Prava doses and Simva 10, 20 and</td>
<td>Compliance was similar for all groups with a range from 90.5-95.3%

Twenty-nine events were serious. No indication what percent were related to treatment.</td>
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<td>and 20 mg, all Prava doses and Simva 10, 20 and 40 mg.
-Rosuva 20 mg statistically better than: Atorva 10, 20 and 40 mg, all Prava doses and Simva 10, 20, 40 and 80 mg.
-Rosuva 40 mg statistically better than all doses of comparator statins.
Rosuva 10, Atorva 40 and Simva 80 approximately equal.</td>
<td>Two patients in the rosuva 80 mg group developed renal failure with one requiring short-term renal dialysis.

The greatest number of patients reporting myalgia, not associated with increases in CK, were in rosuva 80, atorva 20 and 80, prava 20. The lowest reported were simva 40 and rosuva 40.

CK elevations of >10 X ULN, without symptoms, were reported in 1 rosuva 80 and 2 simva 10 patients.

Other ADEs were similar among groups.

Number withdrawing: (Table adapted from article)
<table>
<tr><th>Drug</th><th>Total #</th><th>Due to ADE</th></tr>
<tr><td>A10</td><td>3</td><td>2</td></tr>
<tr><td>A20</td><td>9</td><td>5</td></tr>
<tr><td>A40</td><td>13</td><td>12</td></tr>
<tr><td>A80</td><td>11</td><td>6</td></tr>
<tr><td>P10</td><td>9</td><td>4</td></tr>
<tr><td>P20</td><td>9</td><td>2</td></tr>
<tr><td>P40</td><td>12</td><td>5</td></tr>
<tr><td>R10</td><td>6</td><td>2</td></tr>
<tr><td>R20</td><td>10</td><td>4</td></tr>
<tr><td>R40</td><td>7</td><td>3</td></tr>
<tr><td>R80</td><td>17</td><td>14</td></tr>
<tr><td>S10</td><td>9</td><td>7</td></tr>
<tr><td>S20</td><td>5</td><td>3</td></tr>
<tr><td>S40</td><td>10</td><td>3</td></tr>
<tr><td>S80</td><td>13</td><td>6</td></tr>
</table>
</td>
</tr>
<tr>
<td>Schneck DW, 2003 [20]
R, DB, MC
6 weeks (fixed dose)
n=374

(AstraZeneca)</td>
<td>Atorva 10, 20, 40, or 80 mg daily
OR
Rosuva 5, 10, 20, 40, or 80 mg daily</td>
<td>% LDL-C Reduction from baseline (6 wks)
<table>
<tr><th></th><th>10 mg</th><th>20 mg</th><th>40 mg</th><th>80 mg</th></tr>
<tr><td>Atorva</td><td>38.2</td><td>43.3</td><td>48.4</td><td>53.5</td></tr>
<tr><td>Rosuva</td><td>46.6</td><td>51.7</td><td>56.8</td><td>61.9</td></tr>
<tr><td colspan="5">% Triglyceride Reduction from baseline</td></tr>
<tr><td>Atorva</td><td>17.5</td><td>25.6</td><td>27.2</td><td>34.5</td></tr>
<tr><td>Rosuva</td><td>22.1</td><td>18.4</td><td>25.7</td><td>19.7</td></tr>
<tr><td colspan="5">% HDL-C Elevation from baseline</td></tr>
<tr><td>Atorva</td><td>5</td><td>7.6</td><td>4.1</td><td>2.1</td></tr>
<tr><td>Rosuva</td><td>6</td><td>9.1</td><td>12.3</td><td>9.6</td></tr>
</table>
*5 mg rosuva resulted in a 41.5% reduction in LDL-C, 32.1% reduction in Trigs and 7.4% increase in HDL-C.
The reduction in LDL-C was significantly greater for rosuva for each dose. HDL-C was increased more in the rosuva 40 and 80 mg dose compared to atorva 40 and 80 mg. Trigs were reduced greater in the atorva 80 mg vs. the rosuva 80 mg group.</td>
<td>None of the 3 serious ADE were considered to be related to trials medications. No persistent elevation in LFTs or CK were noted during the trial.

Eight patients on rosuva and 9 patients on atorva withdrew from the trial. Specific reasons for withdrawal were not given.

Medication compliance was not given.</td>
</tr>
</table>

ADE=adverse event, CK=creatine kinase, DB=double-blind, HDL-C=high density lipoprotein, LDL-C=low density lipoprotein, LFTs=liver function tests, MC=multicenter, NR=not reported, OL=open-label, R=randomized, TG=triglycerides, ULN=upper limit of normal

In another trial, the safety and efficacy of rosuvastatin and extended release niacin, alone and in combination, were assessed.[16] In this 24-week, unblinded trial, 270 patients with elevated cholesterol were randomized to 1 of 4 treatment groups. Each of the four groups underwent dose titration at specified time intervals: Group 1: rosuvastatin 10 titrated to 80 mg; group 2: extended release niacin 500 mg titrated to 2

grams daily; group 3: extended release niacin 500 mg titrated to 1 gram daily at which time rosuvastatin 10 mg was added and titrated to 40 mg daily in combination with extended release niacin 1 gram daily; group 4: extended release niacin 500 mg titrated to 1 gram daily at which time rosuvastatin 10 mg was added as a fixed dose with further titration of niacin to 2 grams daily. Rosuvastatin 40 mg daily resulted in a statistically greater LDL-C reduction compared to niacin alone or when niacin was added to 10 mg of rosuvastatin. Addition of niacin to rosuvastatin did not result in any further reduction in LDL-C. With regard to HDL-C, the only statistical difference was a greater elevation in the rosuvastatin 10 and niacin 2 grams daily compared to other groups. There was no statistical difference in triglyceride lowering between groups. Adverse events were reported in 74% of rosuvastatin monotherapy, 90% of niacin monotherapy and 85% of combination therapy. No serious adverse events were considered to be related to treatment. There were no clinically important changes in LFTs or CK in any group. However, on one occasion in the niacin monotherapy group, CK was increased significantly, without symptoms, but resolved with continued treatment.

There are currently no clinical trials demonstrating rosuvastatin's benefit in reducing cardiovascular health outcomes.

Cost

	Lovastatin	Simvastatin	Fluvastatin	Pravastatin	Atorvastatin	Rosuvastatin
Monthly Cost ($) (30 day supply)	20 mg 7.80 40 mg 7.80 80 mg 15.60	10 mg 7.80 20 mg 13.20 40 mg 19.80 80 mg 26.70	20 mg 6.90 40 mg 9.00 80 mg XL 15.30	20 mg 46.80 40 mg 50.70 80 mg 45.60	10 mg 32.70 20 mg 55.20 40 mg 64.80 80 mg 64.80	5 mg 47.10 10 mg 47.10 20 mg 47.10 40 mg 47.10

Conclusion and Recommendations

Rosuvastatin is the most potent statin with regard to its LDL-C lowering abilities. A dose of 10 mg daily produces a mean reduction in LDL-C of 43-49% (data from 6 head to head statin studies). At this time, there are no studies assessing rosuvastatin's benefit with regard to reducing cardiovascular health outcomes.

Rosuvastatin is not a substrate for cytochrome P450 3A4 (CYP 3A4) and therefore is not vulnerable to interactions with potent CYP 3A4 inhibitors. However, there are other interactions and situations that can result in clinically significant increases in rosuvastatin's serum concentrations. As a result, the manufacturer has recommended dose limits or dosing guidance for rosuvastatin in these individuals (e.g. cyclosporine, gemfibrozil, antacids, severe renal impairment, hemodialysis).

To date, the safety and efficacy of rosuvastatin has been evaluated in more than 10,000 patients in controlled clinical trials prior to marketing. In these trials, there did not appear to be differences with regard to liver or muscle toxicity between rosuvastatin and comparator statins in doses up to 40 mg daily. However, there was a higher incidence of 2+proteinuria in those patients receiving 40 mg daily compared to other statins. The FDA did not require the manufacturer to recommend monitoring for proteinuria. However, if unexplained, persistent proteinuria is noted in a patient receiving rosuvastatin 40 mg daily during routine urinalysis, the manufacturer recommends reducing the dose of rosuvastatin.

Since the VA has 3 statins on the National Formulary and the long-term safety (>1 year) of rosuvastatin is unknown, it is recommended that rosuvastatin not be added to the National or VISN formularies. However, it can be considered on a nonformulary basis for those patients receiving potent CYP 3A4 inhibitors who are unable to meet ATP III LDL-C goals on fluvastatin or pravastatin (nonformulary) http://vapbm.org/criteria/Fluva-prava-atorva-r.pdf The initial dose in these patients should be 5 mg daily. It can also be considered in those patients not meeting their LDL-C goals on maximally tolerated doses of other available statins with longer safety records (e.g. lovastatin or simvastatin and then atorvastatin (nonformulary)). The VA Medical Advisory Panel (MAP) has recommended that 20 mg be the maximum daily dose of rosuvastatin in the veteran population until more safety data are available for the 40 mg dose. However, rosuvastatin 40 mg daily can be considered if a provider deems necessary. In those

patients receiving 40 mg daily, baseline and periodic urinary and renal function monitoring are recommended. Finally, rosuvastatin should not be used in Asian individuals until results from the planned pharmacokinetic study of Asians residing in the United States are available.

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Reviewed by: Chester B. Good, M.D., Chairman, Medical Advisory Panel

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