# Safety and Efficacy Comparison of Maximum Dose Simvastatin vs Rosuvastatin

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On June 8, 2011, the U.S. Food and Drug Administration issued a safety announcement recommending limiting the use of the maximum dose of simvastatin (80 mg) due to increased risk of muscle damage. These researchers at the Fargo VA Health Care System share their study results, which compared the maximum dose of rosuvastatin (40 mg) with simvastatin (80 mg) in regards to adverse effects in a mainly elderly male veteran population with multiple comorbid diseases and medications.

Heart disease remains the leading cause of death in the U.S., and studies have shown that elevated low-density lipoprotein cholesterol (LDL-C) is a major cause of coronary artery disease (CAD).[1-5] Lipid-lowering therapy, including simvastatin and rosuvastatin, has an important role in the reduction of LDL-C and primary and secondary prevention of CAD.[6] Within the VA Health Care System (VAHCS), simvastatin plays a major role in lipid management, because it is a formulary agent.

On June 8, 2011, the U.S. Food and Drug Administration (FDA) issued a safety announcement recommending limiting the use of the maximum dose of simvastatin (80 mg) due to increased risk of muscle damage. In addition to the dose limitation, the FDA also required changes in the labeling of simvastatin to add new contraindications, such as combination with cyclosporine and gemfibrozil, and dose limitations for use with certain medications, including amlodipine and ranolazine.[7]

The recommendations of the FDA were based on the results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. The SEARCH trial compared simvastatin 20 mg with simvastatin 80 mg in regards to cardiovascular (CV) and other adverse effects (AEs). Although the trial showed higher doses of simvastatin had a greater reduction in major coronary events, the trial brought to light the increased risk of confirmed myopathy (creatinine kinase [CK] > 10 times the upper limit of normal) in the simvastatin 80-mg dose (1% in simvastatin 80 mg vs 0.03% in simvastatin 20 mg, $P < .0001$).[8]

The maximum doses of rosuvastatin and simvastatin have been compared with each other in studies but not in a head-to-head trial after long-term use (> 6 weeks). This study aimed to compare the maximum dose of rosuvastatin (40 mg) with simvastatin (80 mg) in regards to AEs in a mainly elderly male veteran population with multiple comorbid diseases and medications. Secondary outcomes of this study included comparison of CV events and lipid control.

## METHODS

Study protocol was approved by the local Institutional Review Board and Research and Development Committee. The study, conducted at the Fargo VAHCS in North Dakota, was a retrospective, electronic database review of patients receiving rosuvastatin 40 mg or simvastatin 80 mg. Potential patients were gathered by obtaining a list of all current active prescriptions for rosuvastatin 40 mg or simvastatin 80 mg during October 2010 to January 2011. Patients included in this list could have been on simvastatin or rosuvastatin therapy for any amount of time. These data were then randomized, using a computerized model, and

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**Table 1. Demographic information**

| Variable | Total | Simvastatin | Rosuvastatin | *P* value (simvastatin vs rosuvastatin) |
|---|---|---|---|---|
| Age (mean years ± SD, range) | 66.8 ±9.5, 29-93 | 68.5 ±10.1, 41-91 | 65.2 ±8.7, 29-92 | < .01 |
| Male (%) | 96.7 | 97.2 | 96.1 | = .77 |
| Body mass index (kg/m$^2$) | 31.7 | 31.8 | 31.6 | = .85 |
| Coronary artery disease at baseline (%) | 82.8 | 76.7 | 88.9 | < .01 |
| **Lipid-lowering therapy % (CI)** | | | | |
| Ezetimibe | 3.6 (2.1-6.2) | 1.1 (0.7-4.3) | 6.1 (3.4-10.8) | = .02 |
| Fibrates | 9.4 (6.8-13.0) | 8.9 (5.5-14.1) | 10.0 (6.4-15.4) | = .72 |
| Fish oil | 7.2 (5.0-10.4) | 2.2 (0.7-5.8) | 12.2 (8.2-17.9) | < .01 |
| Niacin | 11.9 (9.0-15.7) | 6.7 (3.8-11.4) | 17.2 (12.4-23.5) | < .01 |
| Bile acid sequestrants | 4.4 (2.7-7.2) | 2.2 (0.7-5.8) | 6.7 (3.8-11.4) | = .07 |
| **Interacting medications % (CI)** | | | | |
| Amiodarone | 1.4 (0.5-3.3) | 1.1 (0.1-4.3) | 1.7 (0.4-5.1) | > .99 |
| Amlodipine | 12.8 (9.7-16.7) | 8.9 (5.5-14.1) | 16.7 (11.9-22.9) | = .03 |
| Clarithromycin | 0.6 (0.0-2.2) | 1.1 (0.1-4.3) | 0.0 (0.0-2.6) | = .50 |
| Diltiazem | 4.4 (2.7-7.2) | 7.2 (4.2-12.1) | 1.7 (0.4-5.1) | = .02 |
| Fluconazole | 0.6 (0.0-2.2) | 0.6 (0.0-3.5) | 0.6 (0.0-3.5) | > .99 |
| Verapamil | 1.1 (0.3-3.0) | 1.7 (0.4-5.1) | 0.6 (0.0-3.5) | = .62 |
| **Diseases % (CI)** | | | | |
| Alcohol abuse | 7.5 (5.2-10.7) | 11.7 (7.7-17.3) | 3.3 (1.4-7.3) | < .01 |
| Diabetes mellitus | 36.4 (31.6-41.5) | 35.0 (28.4-42.2) | 37.8 (31.0-45.1) | = .58 |
| Hypothyroidism | 8.3 (5.9-11.7) | 7.8 (4.6-12.8) | 8.9 (5.5-14.1) | = .70 |
| Liver disease | 1.1 (0.3-3.0) | 1.1 (0.1-4.3) | 1.1 (0.1-4.3) | > .99 |
| Renal disease | 0.8 (5.4-11.1) | 8.3 (5.1-13.4) | 7.2 (4.2-12.1) | = .69 |

CI = confidence interval; SD = standard deviation.

the first 180 eligible patients from each group were included in the study for a total of 360 patients. Data were reviewed for each patient from the period of initiation of the maximum dose statin therapy up to 1 year. A 1-year follow-up period was chosen, based on results of the SEARCH trial in which myopathy occurrence was highest in the first year after initiation.[8]

Patients were eligible for inclusion if they were aged > 18 years and had an active prescription for rosuvastatin 40 mg or simvastatin 80 mg during the prespecified period. Patients were excluded from the study if they had a history of congenital or inherited myopathic disease, such as myasthenia gravis, or a history of congenital or inherited muscular dystrophies listed in their problem list. Comanaged patients (patients receiving primary care outside the VA) were not included as current medications, laboratory work, and adherence to medications were not consistently obtainable.

Demographic information included age, sex, smoking status, and baseline systolic blood pressure at initiation of the maximum dose of the statin. Patient's CAD history or risk equivalent as listed per problem list was collected for calculation of each patient's Framingham risk score. This study assessed the use of additional lipid-lowering therapy, such as fibrates, niacin, ezetimibe, fish oil, or bile acid sequestrants. The use of medications that increase the risk of AEs, such as amiodarone,

**Table 2. Adverse events (N) (%)**

| | Total | Simvastatin | Rosuvastatin | *P* value (simvastatin vs rosuvastatin) |
|---|---|---|---|---|
| **Myalgia** | 65 (18.1) | 37 (20.6) | 28 (15.6) | = .22 |
| **Myositis** | 3 (0.8) | 1 (0.6) | 2 (1.1) | > .99 |
| **Rhabdomyolysis** | 0 | 0 | 0 | > .99 |
| **Hepatic toxicity** | 2 (0.6) | 1 (0.6) | 1 (0.6) | > .99 |
| **Pain scores (median score)[a]** | 4.5 | 5.0 | 4.0 | = .22 |

[a] Pain score base on 0 to 10 numeric scale; 10 = worst.
N = number of patients.

amlodipine, diltiazem, clarithromycin, fluconazole, and verapamil, was also noted. In addition, diseases associated with increased risk of AEs in combination with statin therapy, such as alcohol abuse, diabetes mellitus, hypothyroidism, liver disease, or renal disease, were assessed.

The primary outcome of this study was the rate of AEs, which included myopathy, elevated CK, and hepatic toxicity. Muscle symptoms were assessed using pain data collected from primary care providers (PCPs) and nursing notes. Myopathy was further defined as myalgia (muscle symptoms without CK elevation), myositis (muscle symptoms with increased CK levels), and rhabdomyolysis (muscle symptoms with CK elevation > 10 times the upper limit of normal with CK elevation).[9] All primary care nursing notes contained a section that required the nurse to record assessment of the presence of pain, location, and pain score. Hepatic toxicity was defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 times the upper limit of normal.

Specific interventions to statin therapy were assessed if muscle pains were noted. Interventions included statin discontinuation, statin dosage change, or statin doses held. The percentage of patients that were initiated at the maximum dose of simvastatin or rosuvastatin without titration from a lower dose and associated AEs was measured. To evaluate whether PCPs were monitoring statin therapy appropriately, the percentage of patients with baseline ALT or AST prior to initiation of the maximum-dose statin therapy and number of patients with CK levels drawn after reports of muscle pain were collected.

The study's secondary outcomes included CV events and lipid control. Patients that had been on the maximum dose of statin therapy > 1 year underwent subsequent assessment for incidence of CV events (stroke or acute coronary syndrome). Using demographic data, each patient's Framingham risk score for a CV event was calculated using the National Cholesterol Education Program's online calculator.[10] The Adult Treatment Panel III guidelines were used to determine each patient's target LDL-C levels. Patients with a history of CAD, CAD risk equivalents, or a Framingham score ≥ 20% were defined as at high risk for a CAD event, and the LDL-C target was defined as < 100 mg/dL. Patients with no history of CAD or CAD risk equivalents and a Framingham score ≥ 10% but < 20% were considered at moderate risk for a CAD event, with the LDL-C target defined as < 130 mg/dL. Patients with no history of CAD or CAD risk equivalents and a Framingham score of < 10% were considered at low risk for a CAD event, with the target LDL-C defined as < 160 mg/dL.[6] All lipid values drawn during the 1-year follow-up period were collected. In order to determine lipid values attributed to the maximum dose of statin therapy, the first gathered lipid value for each patient was excluded. In addition, the percentage of patients meeting their lipid targets was calculated based on their Framingham risk score.

Adherence to statin therapy was assessed using the medication refill history of each patient. Adherence was calculated by the total number of doses dispensed divided by the total duration of therapy. The overall percentage of statin discontinuation for any reason was evaluated.

Power analysis was calculated prior to initiation of this study. A total of 141 patients were needed in each group to detect a 10% difference in the rate of myalgia between the groups at a 2-sided significance level of 5% and a power of 80%. The 2-tailed Student's *t* test was used for continuous, roughly normally distributed data. The Wilcoxon rank sum test was applied for continuous variables not normally distributed. The chi-square analysis was used for nominal data with cell sizes > 5 and the Fisher exact test was used for cell

sizes ≤ to 5. A *P* value < .05 was defined as statistically significant.

## RESULTS

A total of 360 patients were included with 180 patients in each group. The researchers noted that patients in the simvastatin group were older than those in the rosuvastatin group (Table 1). The majority of patients (96.7%) were male and had an overall body mass index of 31.7 kg/m$^2$. A higher percentage of patients in the rosuvastatin group had a history of CAD at baseline compared with those in the simvastatin group. Results showed that overall 29.2% of patients were using an additional lipid-lowering therapy, which included fibrates, niacin, ezetemibe, fish oil, or bile acid sequestrants. More patients in the rosuvastatin group than in the simvastatin group (39.4% vs 18.9%, respectively [*P* < .01]) were using additional lipid-lowering therapies. The most common medications used that might have interacted with statin therapy included amlodipine (12.8% of patients overall) and diltiazem (4.4% of patients overall). Overall, 49.7% of patients had at least 1 disease associated with an increased risk of myopathy; the most common was diabetes mellitus.

A higher percentage of patients experienced myalgias in the simvastatin group than in the rosuvastatin group (20.6% vs 15.6%, respectively), although the difference was not statistically significant. There were a few cases of myositis with no rhabdomyolysis identified. There was no difference between the simvastatin and rosuvastatin groups in regards to incidence of myositis, rhabdomyolysis, or hepatic toxicity. Pain scores did not differ between the 2 groups. Interventions were made in 3 patients with myopathy; 1 patient discontinued the statin, 1 patient held the statin dose, and 1 patient changed the statin dose. Of the patients identified with myopathy, 27 (39.7%) had CK levels drawn after reporting muscle pain. Overall, 58.6% of patients had baseline ALT or AST drawn before initiation of the maximum dose of statin therapy, and there was no difference between the simvastatin and rosuvastatin groups (Table 2).

**Table 3. Median lipid values**

| | Total | Simvastatin | Rosuvastatin | *P* value (simvastatin vs rosuvastatin) |
|---|---|---|---|---|
| N | 305 | 148 | 157 | |
| Total cholesterol (mg/dL) | 165.2 | 168.4 | 164.6 | = .96 |
| Low-density lipoprotein cholesterol (mg/dL) | 92 | 92.3 | 92 | = .91 |
| High-density lipoprotein cholesterol (mg/dL) | 41 | 40.5 | 41 | = .96 |
| Triglycerides (mg/dL) | 131 | 133 | 130 | = .98 |

N = number of patients.

Overall, the percentage of patients that had a CV event after 1 year on the maximum dose statin therapy was 5.3%. The simvastatin group had a much higher incidence of CV events compared with rosuvastatin (8.3% vs 2.2%, respectively [*P* = .02]). Following exclusion of the initial lipid level collected, the researchers noted that only 305 of the 349 patients with lipid values collected had additional lipid levels drawn during the 1-year follow-up period. Median lipid values were calculated vs mean lipid values, because the data were not normally distributed. Median lipid values did not differ between groups (Table 3). Patients were divided into risk categories based on their Framingham risk scores to assess LDL-C goal. The percentage of patients meeting the LDL-C goal overall was 67.5%. The percentage of patients in the simvastatin and rosuvastatin groups were similar across the 3 risk categories. The majority of patients on the maximum dose of statins were in the high-risk group (269 out of 305 patients with measured lipid levels), although of these patients, 64.7% of patients overall were meeting their LDL-C goal (Table 4).

The adherence rate overall was 87.7%; the simvastatin group had a slightly lower rate at 85.7% vs 90.8% in the rosuvastatin group, although the difference was not statistically significant. The percentage of patients discontinuing statin therapy overall was higher in the simvastatin group compared with the rosuvastatin group (27.2% vs 9%, respectively [*P* < .01]). More patients in the rosuvastatin group were started on the maximum dose of therapy without dose titration than those in the simvastatin group (30% vs 20%, respectively [*P* < .05]).

**Table 4. Patients meeting LDL-C targets (%)**

| | Patients (N) | Overall % | Simvastatin % | Rosuvastatin (%) | *P* value (simvastatin vs rosuvastatin) |
|---|---|---|---|---|---|
| All subjects | 305 | 67.5 | 65.5 | 69.4 | = .47 |
| Low risk: Framingham < 10% Target level < 160 mg/dL | 9 | 100 | 100 | 100 | > .99 |
| Moderate risk: Framingham ≥ 10% to < 20% Target level < 130 mg/dL | 27 | 85.2 | 86.7 | 83.3 | > .99 |
| High risk: CAD or CAD risk equivalent or Framingham ≥ 20% Target level < 100 mg/dL | 269 | 64.7 | 61.7 | 67.4 | = .33 |

CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol; N = number of patients.

Of the patients initiated on the maximum dose statin therapy, 4 patients in the simvastatin group developed myopathy vs 11 patients in the rosuvastatin group, although this difference was not statistically significant.

## DISCUSSION

Myopathy is a clinically significant AE associated with statins. In this study, the overall myopathy (myalgia, myositis, and rhabdomyolysis) rate was 18.9%, and no statistical difference was found in the incidence of myopathy between the maximum doses of simvastatin and rosuvastatin. Myalgias occurred in 20.6% of simvastatin patients vs 15.6% of rosuvastatin patients, although this difference was not statistically significant. The Prediction of Muscular Risk in Observational Conditions (PRIMO), a large observational trial, including just under 8,000 patients on high-dose statins (simvastatin, atorvastatin, fluvastatin, and pravastatin) reported an overall incidence of muscular symptoms of 10.49%.[11] The SEARCH trial compared simvastatin 80 mg with simvastatin 20 mg and found the incidence of myopathy to be 1% in the simvastatin 80-mg group vs 0.03% in the simvastatin 20-mg group ($P < .0001$).[8] It is difficult to compare myopathy rates from this study with the SEARCH trial results, because it used a myopathy definition of CK > 10 times the upper limit of normal, whereas in this study, myopathy is a broad term for muscle symptoms. It should be stressed that a more uniform definition of myopathy would be beneficial for future studies comparing myopathy incidence in statin therapy.

Only 37.9% of patients in this study had CK levels drawn after reporting muscle pain, and interventions were made in only 3 of the 68 patients with reports of myopathy. Some studies recommend that clinicians should first draw a CK level and rule out other causes when a patient reports myopathy. If muscle pain is intolerable or the patient's CK level is moderately to severely elevated, the patient should discontinue the statin. Once muscle symptoms resolve, the patient can be rechallenged with the same statin at a lower dose, use alternative dosing strategies, or start a less myotoxic statin. No firm guidelines or recommendations for statin-associated myopathy exist. Institutions may develop algorithms using current literature to guide clinicians in the monitoring and management of myopathy.[9,12-14] The development of such an algorithm may benefit providers within the Fargo VAHCS and assist in a more consistent treatment plan for statin-associated myopathy.

Cardiovascular events after 1 year of the maximum dose of statin therapy were higher in the simvastatin group vs the rosuvastatin group. This difference may be explained by the difference in the percentage of patients discontinuing statin therapy. Significantly more patients in the simvastatin group discontinued their statin (27.2% in the simvastatin group vs 9% in the rosuvastatin group [$P < .01$]). Studies have demonstrated that limiting discontinuation and maintaining adherence to statin therapy is related to fewer CAD-related hospitalizations and emergency department visits.[15,16]

The median LDL-C value for both simvastatin and rosuvastatin was 92 mg/dL, which is similar to that found in the Comparison of the Efficacy and Safety of Rosuvastatin

Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR) trial (mean LDL-C 103 mg/dL in the simvastatin group and 87 mg/dL in the rosuvastatin group). The percentage of patients meeting their lipid targets in this study was similar between the 2 groups (65.5% of simvastatin patients vs 69.4% of rosuvastatin patients), although this result is somewhat lower than that of the STELLAR trial (82.2% in the simvastatin group vs 89.2% in the rosuvastatin group [$P = .01$]). The difference between the studies may be due to the duration of follow-up, because the STELLAR trial only evaluated lipid values up to a 6-week duration.[17] Also, this study had a high proportion of patients defined as high risk for CV events with LDL-C targets < 100 mg/dL.

## LIMITATIONS

The limitations of this study included that it was a retrospective chart review, confounding variables were not able to be controlled, and the majority of patients were male and aged > 65 years, which limited the study's external validity. Myopathy findings were based on subjective pain scales, and only primary care notes were reviewed in this study. The primary care nursing note asked only about the presence of pain, but many patients may have responded differently to a direct question regarding the presence of muscle pain or weakness.

This study identified areas for improvement within the Fargo VAHCS. Use of consistent myopathy terminology and the potential development of a facility-specific algorithm may assist providers in the diagnosis and management of statin-associated myopathy. In addition, continued follow-up and adjustment of statin therapy for patients who do not meet their lipid targets may improve their CV outcomes.

## CONCLUSION

The trial found no difference in the incidence of myopathy between the maximum dose of simvastatin and rosuvastatin. Cardiovascular events were higher in the simvastatin group than in the rosuvastatin group. Lipid control was similar between the 2 groups. Prospective, randomized, controlled trials with the use of a standardized definition of myopathy are warranted to verify the primary outcome of this study. ●

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