Comparative Efficacy of Ezetimibe/Simvastatin, Rosuvastatin, and Atorvastatin in Uncontrolled Hyperlipidemia Patients

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Objective: Treatment of dyslipidemia in high-risk patients specifies a low-density lipoprotein (LDL) cholesterol <100 mg/dL. The efficacy of higher-potency regimens in clinical practice in patients who have not achieved their LDL goal on generic therapy is not well characterized. The primary objective of this study was to determine the LDL-lowering efficacy of higher-potency strategies (ezetimibe/simvastatin, rosuvastatin, and atorvastatin) in high-risk patients who were switched from simvastatin therapy. Secondary objectives were to evaluate patient adherence to these therapies, determine the efficacy of these interventions on other lipid parameters, and define the incidence of adverse effects.

Study Design: Retrospective data analysis derived from the Veterans Affairs Health Care System VISN 21 over a 3-year time period.

Methods: Lipid data were assessed prior to and within 2 to 6 months following the conversion from simvastatin. Adherence to therapy was determined by medication refill data.

Results: Treatment with ezetimibe/simvastatin resulted in significantly greater reductions in LDL compared with rosuvastatin or atorvastatin (37 vs 25 and 26 mg/dL, respectively; P <0.05). Adherence to therapy was 51% of all patients studied. All treatments significantly lowered total cholesterol, high-density lipoprotein, and triglycerides when compared with simvastatin. There was no difference between treatment groups in the number of adverse events.

Conclusions: At the doses used in this population, ezetimibe/simvastatin resulted in greater LDL reductions than rosuvastatin or atorvastatin. The clinical impact of these differences is as yet undetermined.

(Am J Manag Care. 2011;17(8):538-544)

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Approximately 105 million adults in the United States, 55% of the adult population, have a total cholesterol level of 200 mg/dL or higher.[1] Cholesterol levels, specifically low-density lipoprotein (LDL) levels, are a major independent risk factor for the development and progression of atherosclerosis, and have long been linked to an increased risk of death from major coronary events.[2]

The third report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), published in 2002, presented a set of evidence-based guidelines to manage hyperlipidemia. NCEP ATP III recommended individualized LDL goals based on a patient's risk factors. According to these guidelines, patients have an LDL goal of less than 100 mg/dL (with an optional goal of <70 mg/dL) if they have a clinical diagnosis of coronary heart disease (CHD) or an equivalent risk factor.[3] CHD-equivalent risk factors include symptomatic carotid artery disease (CAD), diabetes, peripheral arterial disease, a history of abdominal aortic aneurysm, or multiple risk factors that confer a 10-year risk for CHD of >20% using the Framingham coronary prediction algorithm.[3]

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HMG-CoA reductase inhibitors (statins) lower cholesterol by reducing cholesterol production in the liver and upregulating LDL receptors.[4] The efficacy of statins in lowering LDL cholesterol has been well established in the literature, and they are the standard of treatment for patients with elevated LDL cholesterol.[5] The LDL goal of <100 mg/dL can be achieved in 25% to 50% of high-risk patients using moderate potency statins, such as simvastatin, at usual doses.[6] Patients at higher risk and, consequently, with more stringent lipid goals, have caused healthcare providers to search for more potent lipid-lowering agents.

High-potency statins, or combination therapy with a statin and a cholesterol absorption inhibitor such as ezetimibe, are alternatives which have been shown to be more potent than moderate-potency statins in reducing LDL cholesterol.[7] Multiple studies have compared lipid-lowering efficacy of several of these higher-potency therapies. For example, in a randomized comparison study, rosuvastatin was found to be more potent than atorvastatin, simvastatin, or pravastatin in lowering LDL.[8] Similarly, the addition of ezetimibe to statin therapy was shown to result in significant reductions in LDL,[9] and, in direct comparison with rosuvas-

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tatin, ezetimibe/simvastatin was more potent in reducing LDL and achieving target levels.[10] However, no study has examined the clinical efficacy of the 3 most commonly used higher-potency interventions in a high-risk veteran population.

The purpose of this study was to determine the LDL-lowering efficacy of 3 lipid-lowering therapies (ezetimibe/simvastatin, rosuvastatin, and atorvastatin) in patients switched from simvastatin therapy when dosed at least 40 mg per day. In addition, the effect of these therapies on non-LDL lipid parameters, as well as the incidence of adverse effects, was evaluated.

Take-Away Points

In a Veterans Administration population, low-density lipoprotein (LDL)-lowering in patients switched from generic simvastatin was greater with ezetimibe/simvastatin than atorvastatin or rosuvastatin without any difference in side effects. Adherence to therapy was only 51% and had a marked effect on the efficacy of LDL lowering. Thus:

- The greatest effect on LDL lowering is achieved using combined statin and cholesterol absorption inhibition.
- Adherence is crucial in the effective treatment of dyslipidemias.
- Adverse events are infrequent.
- The impact of these differences on cardiovascular events is, as yet, undetermined.

METHODS

Study Design

This study was approved by the Institutional Review Board of the Veterans Affairs (VA) Northern California Health Care System. The study design was a retrospective electronic database review using data from the 6 VA facilities within the VISN 21 region, serving northern Nevada, northern California, and Hawaii. Demographic, diagnostic, prescription, and procedural data were organized and analyzed using Microsoft SQL tables. The data collected prior to conversion were used to determine baseline characteristics, including cardiovascular (CV) risk and medication adherence.

Patients

Veterans Affairs patients were included if they were categorized as high risk by ATP III criteria, received at least 1 prescription of simvastatin at 40 mg/day or greater, or had an LDL measurement >100 mg/dL on simvastatin, followed within 120 days by a prescription for 1 of the 3 study medications (ezetimibe/simvastatin, rosuvastatin, or atorvastatin). Patients were excluded from the final analysis if they did not have a recorded LDL within 6 months of conversion, were taking ezetimibe prior to conversion, or had a creatinine clearance <30 mL/min or a >10% change in body mass index (BMI) between time of conversion and lipid panel assessment.

Risk Assessment

CV risk was defined as the presence of at least 1 diagnosis code (*ICD-9*) for CHD or a CHD risk equivalent in the 2 years before conversion, or a calculated 10-year CHD risk of >20% at the time of conversion using the Framingham risk score.[11]

Adherence Assessment

Adherence was assessed using a medication possession ratio (MPR), calculated by dividing the total days supply of medication received by the total dispensing time period. A ≥80% use threshold was defined as positive adherence. Adherence was assessed both while the patient was on simvastatin and while on the study medication in the first 6 months after conversion.

Efficacy Assessment

Simvastatin lipid-lowering efficacy was determined using the LDL cholesterol obtained at the time closest to conversion. Study medication lipid-lowering efficacy was determined using the last LDL level collected within the first 6 months of conversion. Other lipid measurements (total cholesterol [TC], high-density lipoprotein cholesterol [HDL], and triglycerides) were obtained at the same measurement time as LDL.

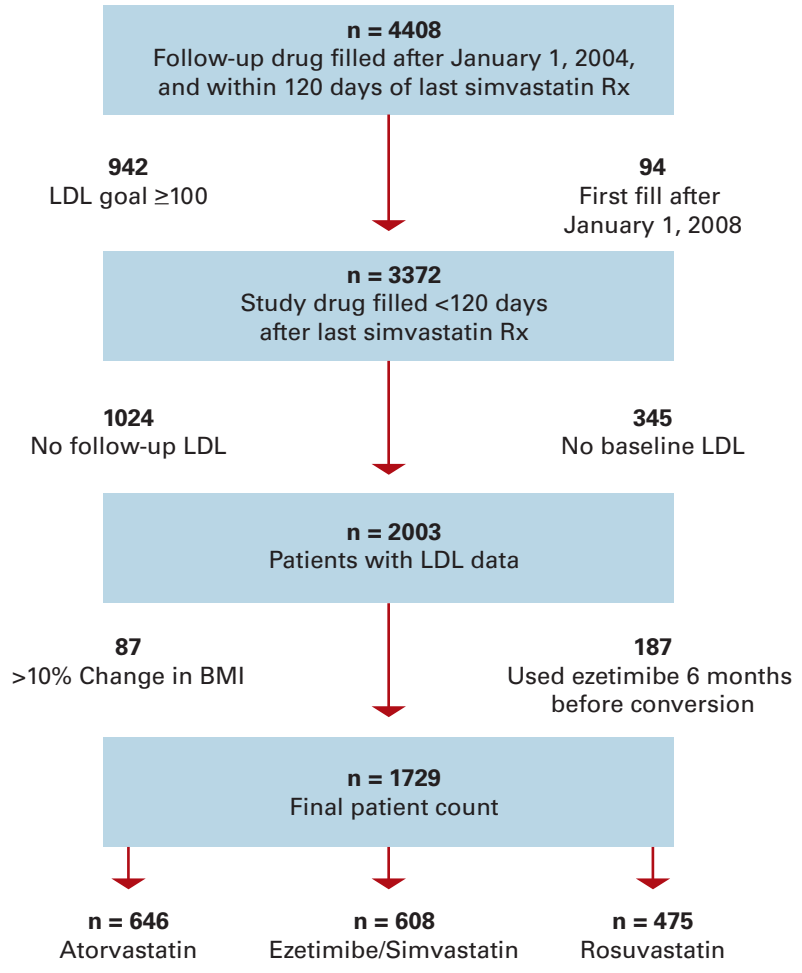
Adverse Events

Adverse events included laboratory abnormalities in liver transaminases (AST and ALT), renal function (blood urea nitrogen [BUN] and creatinine), and myopathy (creatine kinase [CK]). Laboratory data were converted from continuous to nominal data by defining each variable as either normal or abnormal based on normal values in the laboratory.

Statistical Analysis

The primary efficacy variable was the mean LDL cholesterol at follow-up in all patients. Secondary efficacy variables included HDL cholesterol, triglycerides, and the ratio of total and LDL cholesterol to HDL cholesterol (TC/HDL and LDL/HDL). Secondary end points were adverse events per 100 patient years. Mean LDL levels were compared in groups before and after conversion using the Student's *t* test. Baseline characteristics and follow-up laboratory data were compared across groups using the Kruskal-Wallis 1-way ANOVA and Dunn's method for pairwise comparison. Chi-square analysis was used for nominal data with large sample sizes, and the Fisher exact test was used for small sample sizes. A *P* value <0.05 was used to determine significance.

Figure 1. Diagram of Patient Inclusion/Exclusion Criteria and Selection for Analysis



BMI indicates body mass index; LDL, low-density lipoprotein.

RESULTS

Patient Characteristics

Figure 1 shows how the exclusion criteria were applied to our patients. A total of 4408 patients had a prescription for ezetimibe/simvastatin, rosuvastatin, or atorvastatin within 120 days of their last simvastatin prescription fill. After including only high-risk patients with an LDL goal of <100 mg/dL and excluding patients with greater than 10% change in BMI and those who were receiving ezetimibe before conversion, 1729 patients were left for evaluation (608 ezetimibe/simvastatin, 475 rosuvastatin, and 646 atorvastatin).

Table 1 shows the baseline characteristics of the patient population. At baseline, all groups were similar in regard to age, BMI, gender, ethnicity, and the Charlson Comorbidity Index. The mean pre-conversion cholesterol and triglyceride levels in patients on simvastatin were not different between the groups, although patients converted from simvastatin to rosuvastatin were taking a lower average simvastatin dose than those either switched to ezetimibe/simvastatin or atorvastatin (69 vs 72 and 73 mg respectively; P <0.05).

Lipid-Lowering Efficacy

The average doses used were 9/64, 18, and 68 mg for ezetimibe/simvastatin, rosuvastatin, and atorvastatin, respectively, representing 80%, 45%, and 85% of maximum recommended doses. Based on published efficacy data,[2,12,13] these doses would be expected to result in approximately 58%, 54%, and 51% reductions in LDL from untreated levels. Figure 2 shows the average LDL value at baseline and follow-up, as well as the average reduction in LDL, in the 3 groups. There was no difference in LDL at baseline between the 3 groups. The ezetimibe/simvastatin group had a significantly lower LDL at follow-up than either the atorvastatin or rosuvastatin groups (84 compared with 94 mg/dL each, respectively; P <0.05). The average change in LDL for the ezetimibe/simvastatin group was also significantly greater than the other 2 groups (37 vs 25 and 26 mg/dL, respectively; P <0.05), corresponding to percentage reductions of 31% with ezetimibe/simvastatin compared with 22% and 21% with atorvastatin and rosuvastatin respectively (P <0.05). The most frequently administered doses of ezetimibe/simvastatin were 10/80 and 5/40 mg (62% and 24% of total doses), while for atorvastatin they were 80 and 40 mg (74% and 17%), and for rosuvastatin 20 and 10 mg (46% and 31%). At the doses used, a significantly higher percentage of patients had an LDL <100 mg/dL with ezetimibe/simvastatin compared with rosuvastatin or atorvastatin (79% vs 65% each respectively; P <0.05). While there were no significant changes in HDL, all treatments significantly reduced triglycerides, total cholesterol, the LDL:HDL ratio, and the TC:HDL ratio when compared with simvastatin monotherapy. Consistent with the greater reduction in LDL, ezetimibe/simvastatin demonstrated significantly greater reductions in total cholesterol and the ratios of LDL to HDL and total to HDL cholesterol than atorvastatin and rosuvastatin (Table 2).

Adherence

Adherence is a major concern with both the veteran and general population. In this cohort, only 51% of patients met ad-

Table 1. Baseline Characteristics

	E/S	Atorvastatin	Rosuvastatin	*P*
Subjects, n (mean ± SD)	608	646	475	NS
Age, yrs	66 ± 9	66 ± 10	65 ± 9	NS
Simvastatin dose, mg	72 ± 17	73 ± 17	69 ± 22	<.05[a]
Body mass index	31 ± 6	30 ± 7	31 ± 5	NS
Charlson Comorbidity Index	1.5 ± 0.9	1.5 ± 1.2	1.4 ± 1.1	NS
LDL	121 ± 28	120 ± 35	119 ± 35	NS
HDL	40 ± 10	41 ± 10	39 ± 10	NS
Triglycerides	172 ± 107	177 ± 124	199 ± 289	NS
Total cholesterol	194 ± 35	196 ± 44	194 ± 44	NS
Gender, male %	97	96	98	NS
Ethnicity %				NS
African American	13	11	8	
Asian	6	6	13	
Hispanic	8	5	8	
Caucasian	72	77	71	

E/S indicates ezetimibe/simvastatin; HDL, high density lipoprotein; LDL, low density lipoprotein.
[a]*P* <.05 rosuvastatin <atorvastatin.

herence criteria both with simvastatin at baseline and while on study medication. Compared with the entire cohort, patients who were adherent to therapy before and after conversion (n = 870) exhibited a significantly lower final LDL concentration than the entire cohort (62, 73, and 72 mg/dL for ezetimibe/simvastatin, atorvastatin, and rosuvastatin, respectively), while those who were nonadherent at follow-up showed only an average reduction in LDL of 24 mg/dL with ezetimibe/simvastatin. These data show the remarkable, but not unexpected, effect that adherence has on the extent of LDL reduction with therapy. Finally, despite the fact that adherence was greater in those patients taking atorvastatin than ezetimibe/simvastatin or rosuvastatin (57% vs 47% and 45%, respectively; *P* <0.05), this difference did not translate into greater LDL reductions.

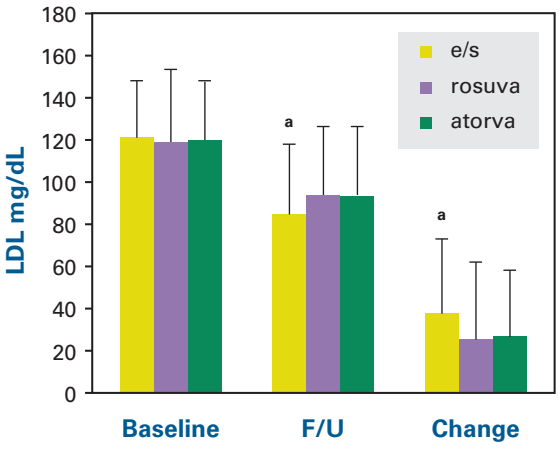
Adverse Effects

There were no significant differences in indices of liver or renal function, or elevation of CK, between the groups at baseline or at follow-up. The incidence of abnormalities in BUN and creatinine was not different from that in simvastatin.

DISCUSSION

This study demonstrated that ezetimibe/simvastatin was more effective than either atorvastatin or rosuvastatin in reducing LDL cholesterol in patients who were switched from simvastatin monotherapy. However, only half the patients prescribed therapy had adherence >80% with both simvastatin and subsequent therapy. Despite differences in LDL efficacy, there were no significant differences in HDL or adverse events.

Figure 2. LDL (mg/dL) at Baseline, Follow-up (F/U), and the Change (Reduction) in LDL for the 3 Groups



Atorva indicates atorvastatin; e/s, ezetimibe/simvastatin; LDL, low-density lipoprotein; rosuva, rosuvastatin.
[a]*P* <.05 e/s vs other groups.

Therapeutic Efficacy

Simvastatin has abundant data regarding efficacy and impact on cardiovascular outcomes.[14] Consequently, and because

Table 2. Follow-up Lipid Data

	E/S	Atorvastatin	Rosuvastatin	*P*
Subjects, n (mean ± SD)	608	646	475	
Dose (mg)	9/64	68	18	
LDL (mg/dL)	84 ± 34	94 ± 33	94 ± 33	< .05[a]
Change in LDL (mg/dL)	–37 ± 36	–26 ± 32	–25 ± 37	<.05[a]
HDL (mg/dL)	40 ± 10	41 ± 10	39 ± 10	NS
Change in HDL (mg/dL)	–0.67 ± 7.21	–0.89 ± 6.69	–0.37 ± 6.64	NS
Change in LDL:HDL ratio	–0.95 ± 1.12	–0.62 ± 0.99	–0.72 ± 1.70	<.05[a]
Triglycerides (mg/dL)	158 ± 127	152 ± 103	177 ± 170	<.05[b]
Total cholesterol (mg/dL)	153 ± 43	164 ± 41	165 ± 41	<.05[a]
Change in total cholesterol:HDL ratio	–0.97 ± 1.76	–0.73 ± 1.53	–0.84 ± 2.65	<.05[a]

E/S indicates ezetimibe/simvastatin; HDL, high density lipoprotein; LDL, low density lipoprotein.
[a] *P* <.05 e/s vs atorvastatin and rosuvastatin.
[b] *P* <.05 rosuvastatin vs e/s and atorvastatin.

it is cost-effective as a generic formulation, it has become the primary statin therapy in the VA healthcare system.[15] However, the efficacy of simvastatin in achieving LDL goals in high-risk patients, defined as those with cardiac or peripheral vascular disease, diabetes, or high Framingham risk, is limited.[16] Thus, a significant number of patients require more potent therapy to achieve these goals. Currently, the choices for advanced therapy include the combination of ezetimibe and simvastatin as well as monotherapy with rosuvastatin or atorvastatin.

Although there are published data regarding the efficacy of statin and other therapy for dyslipidemias, there are no trials which have compared ezetimibe/simvastatin with both rosuvastatin and atorvastatin in 1 population. When compared with atorvastatin, ezetimibe/simvastatin has shown greater efficacy in LDL reduction, generally resulting in a 10% difference in LDL reduction across doses.[13] When compared with rosuvastatin, ezetimibe/simvastatin has also shown greater efficacy in LDL-lowering across doses.[10] For example, 1 European study of 618 patients switched from existing therapy to either ezetimibe/simvastatin 10/20 or rosuvastatin 10 mg showed 27.7% vs 16.9% reduction in LDL.[17] Similarly, a meta-analysis of 14 trials of individual, but not comparative, studies showed that ezetimibe/simvastatin had greater efficacy than rosuvastatin in lower to middle doses, but this difference disappeared at the highest recommend doses.[18]

Despite demonstrated efficacy in lowering LDL, there are limited data on the impact of ezetimibe/simvastatin on cardiovascular outcomes. In trials examining progression of carotid intimal medial thickness (IMT), ezetimibe/simvastatin was not shown to be superior to simvastatin alone despite greater LDL reductions,[19] and was inferior to a combination of simvastatin and niacin.[20] In preliminary results, ezetimibe/simvastatin demonstrated a 17% reduction in major atherosclerotic events compared with placebo in patients with chronic kidney disease, although there was no comparison to an active treatment arm.[21] Thus, at present, definitive data regarding the utility of ezetimibe/simvastatin on cardiovascular outcomes in the general population is pending the outcome of an ongoing large trial.[22]

When compared with atorvastatin, rosuvastatin is more potent, both in LDL reduction and in the percent of patients reaching LDL goals. For example, the Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin Simvastatin and Pravastatin Across Doses (STELLAR trial) showed that rosuvastatin 10 to 80 mg exhibited a 4.7% greater reduction in total cholesterol when compared with atorvastatin 10 to 80 mg and 18.7% more than pravastatin 10 to 40 mg.[8] The rosuvastatin 20 to 40 mg group also had the highest proportions of patients who reached NCEP ATP III LDL goals. In the current study, rosuvastatin was less frequently used at or near its maximal dose when compared with ezetimibe/simvastatin, thereby potentially limiting its comparative efficacy in lowering LDL.

Adherence

Adherence to medications, as determined by the medication possession ratio, was not optimal and had a clear effect on the efficacy of LDL reduction. Notably, approximately half the patients in this cohort were not adherent with either simvastatin or subsequent therapy. Adherence to therapy has been extensively studied, and this rate of adherence is similar to that in large populations in both primary and secondary prevention.[23-25] Many factors, such as age, polypharmacy, and lack of social support have been suggested as reasons for poor

adherence[26] and may have been present in this population. However, other known factors, such as drug costs and side effects, should not have been material in this study, as medications are low cost or free within the VA and the incidence of adverse events was low in this population.

Adverse Events

Consistent with prior data, the incidence of adverse events, including elevation in liver enzymes, creatine phosphokinase, or renal function was low and not different between the 3 therapies. Notably, there were no instances of myopathy or hepatic injury, nor a significant increase in abnormal laboratory values from simvastatin monotherapy.

Limitations

As a retrospective database study, there was no randomization of patients and the reasons for selection of a specific therapy in switching from simvastatin are unknown. Hence, there could be unrecognized confounding variables which biased the selection of therapy. In addition, only 39% of potentially eligible patients were included in the final analysis due to entry criteria and incomplete data. Finally, due to the small sample size, this study was not adequately powered to assess any differences in CV outcomes across groups.

CONCLUSION

In the doses used in this study, ezetimibe/simvastatin had greater LDL reductions than either rosuvastatin or atorvastatin in patients switched from simvastatin. Similarly, there were greater reductions in total cholesterol and the ratios of TC:HDL and LDL:HDL, without differences in HDL. Adherence to therapy was significantly related to LDL reduction, with a reduction in LDL approximately 35 mg/dL greater in adherent compared with nonadherent patients. There were no differences in adverse events in this population. Whether these differences in LDL-lowering efficacy will result in differences in CV outcomes in larger populations is yet to be tested.

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Funding Source: None reported.

Author Disclosures: Dr Schaefer reports receiving lecture fees for speakers bureaus from Merck and AstraZeneca. The other authors (AF, JLM, RAM, JRL) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (AF, JLM, RAM, JRL, SS); acquisition of data (AF, JLM, SS); analysis and interpretation of data (AF, JLM, RAM, JRL, SS); drafting of the manuscript (AF, SS); critical revision of the manuscript for important intellectual content (AF, JLM, RAM, JRL); statistical analysis (AF, JLM); provision of study materials or patients (SS); administrative, technical, or logistic support (SS); and supervision (JLM, SS).

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