Effectiveness and Cost-effectiveness of Rosuvastatin, Atorvastatin, and Simvastatin Among High-risk Patients in Usual Clinical Practice

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Abstract

Background: Assessments of the effectiveness and cost-effectiveness of treatment with statins in high-risk patients in routine clinical practice are needed. The objective of the present study was to estimate the clinical effectiveness and cost-effectiveness of rosuvastatin compared with atorvastatin or simvastatin among high-risk patients as treated in routine clinical practice.

Methods: Patients aged 18 to 79 years with coronary heart disease (CHD) or equivalent who initiated treatment with atorvastatin, rosuvastatin, or simvastatin were included. Primary outcome variables were the percent reduction in low-density lipoprotein cholesterol (LDL-C), achievement of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C goal, treatment costs, and cost-effectiveness. Regression models were used to adjust outcome measures for age, sex, CHD, baseline LDL-C, and therapy duration. A decision analytic model was used to assess incremental cost-effectiveness.

Results: Of the 775 eligible patients, rosuvastatin patients had higher baseline LDL-C levels (156 mg/dL vs 142 mg/dL or 137 mg/dL, respectively) compared with atorvastatin or simvastatin. Adjusted for baseline factors, percent LDL-C reduction was significantly greater with rosuvastatin versus atorvastatin or simvastatin (37% vs 28% or 27%, respectively; $P < .05$). The estimated percentage of patients attaining NCEP ATP III goal was higher ($P < .05$) for rosuvastatin (69.7%) compared with atorvastatin (54.8%) or simvastatin (51.2%), adjusted for baseline characteristics. Rosuvastatin patients also had the lowest annualized treatment costs ($934 vs $1050 or $1545 for atorvastatin or simvastatin). Rosuvastatin was more effective and less costly than atorvastatin and at current branded and generic prices of simvastatin. A 60% to 68% discount from simvastatin branded price was needed to achieve equivalent cost-effectiveness as rosuvastatin.

Conclusions: In clinical practice, rosuvastatin is more effective and cost-effective in lowering LDL-C and in attainment of ATP III LDL-C goals compared with atorvastatin or simvastatin among high-risk patients.

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Coronary heart disease (CHD) continues to be the leading cause of mortality and morbidity in the United States.[1] CHD has been identified as 1 of the 5 most costly health conditions to US employers, with a total annual cost of $142 billion.[1,2] A wealth of evidence from clinical trials and meta-analyses of trial results clearly demonstrated that statin therapy lowers total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels, thereby reducing CHD risk and total mortality.[3-15] More recently, clinical data demonstrated that more intensive lipid lowering provides additional clinical benefits.[14]

Evidence-based guidelines issued by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) underline the importance of hyperlipidemia treatment with an aggressive LDL-C goal of <100 mg/dL for high-risk patients.[16] Moreover, updated optional recommendations to the ATP III guidelines, published in July 2004, now recommend an optional LDL-C goal of <70 mg/dL in very high-risk patients.[17]

Despite the proven morbidity and mortality benefit of cholesterol reduction and the

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presence of nationally accepted NCEP guidelines, there is evidence of inadequate hypercholesterolemia management.[18] Recent observational studies suggest that many patients who are prescribed statin therapy do not achieve the NCEP goal for LDL-C reduction.[19-21] However, there is limited evidence on the effectiveness and the cost-effectiveness of statins in clinical practice, outside of the randomized clinical trial setting, especially among high-risk patients. Additionally, there has been no comparison in high-risk patients of real-world effectiveness between rosuvastatin, atorvastatin, and simvastatin. Because of limited data on real-world effectiveness for different statins among high-risk patients, the objective of the present study was to estimate the clinical effectiveness and cost-effectiveness of rosuvastatin compared with atorvastatin or simvastatin among high-risk patients in the community who were treated by their primary care physicians.

Methods

In this retrospective study, patients between the ages of 18 and 79 years treated in 1 of 500 physician offices in the Midwest (Indiana, Michigan, Kentucky, and Ohio) and who had a diagnosis of CHD and/or CHD risk equivalents (according to NCEP ATP III guidelines)[16] were eligible for inclusion. CHD risk equivalents were defined as a diagnosis of any 1 of the following conditions: atherosclerosis, ischemic cerebrovascular disease, cerebral atherosclerosis, stroke, peripheral vascular disease, abdominal aortic aneurysm, or diabetes. Additionally for patients to be included in the study, they had to meet the following criteria: (1) at least 1 complete lipid panel result before and after initiating statin therapy; (2) initiated statin therapy between July 1, 2001, and April 31, 2005; (3) no dyslipidemic medications (including bile acid sequestrants, fibric acid, nicotinic acid, ezetimibe, statins) in the 6 months before statin treatment; and (4) no switching to other statins during the study period. Titration of the statin therapy was permitted. Duration of statin therapy was limited to ≤18 months to minimize differences in the follow-up periods for rosuvastatin compared with atorvastatin and simvastatin.

The baseline lipid results were defined as the lipid panel obtained closest to (up to 90 days before) the start date of statin therapy. If lipid panel results were not available within 90 days before initiating statin therapy, the patient was excluded from the study. The final lipid results were defined as the lipid panel obtained closest to the end of the study period while the patient was still taking the same statin as at the start of treatment. The final lipid panel had to be obtained at least 4 weeks after initiating statin therapy. The study was limited to patients who were taking rosuvastatin, atorvastatin, or simvastatin, because these are the high-efficacy statins suitable for managing high-risk CHD patients. A total of 775 patients met the eligibility criteria and were included in the study. The following data were abstracted from the patient medical record by the office nurse: diagnosis of CHD or CHD risk equivalent diagnoses, statin therapy type, starting dose, units and frequency, lipid panel results and dates, age, sex, family history of CHD, height, weight, and most recent blood pressure measurement.

Outcomes of interest were the percentage change in lipid parameters and the proportion of patients attaining ATP III LDL-C <100 mg/dL goal and the NCEP 2004 optional aggressive LDL-C <70 mg/dL goal for very high-risk patients ("very high-risk patient" was defined as having CHD or CHD risk equivalent with a diagnosis of diabetes, acute coronary syndrome, or metabolic syndrome).[16,17] Univariate analysis of variance was conducted to detect a difference between rosuvastatin and atorvastatin, and between rosuvastatin and simvastatin in percentage change in the lipid parameters and in the proportion of patients attaining NCEP LDL-C goal levels. Rosuvastatin was used as the reference drug because clinical trials have shown it to be the most efficacious statin monotherapy. Observed change in lipid parameters was derived as the percent change from baseline to final lipid panel results for each patient. The average percent LDL-C change achieved by each statin was computed and differences detected by Student's *t* test for pairwise comparison. NCEP goal attainment was derived as the

proportion of patients with LDL-C levels <100 mg/dL for ATP III goal attainment and LDL-C levels <70 mg/dL for very high-risk patients for the 2004 NCEP guideline update. Multivariate regression analyses were used to adjust for baseline differences among the statin groups, including baseline LDL-C level, age, sex, diagnosis of CHD, and length of statin treatment. Hypertension was not examined in the regression model because it was one of the components in the classification of patients as high CHD risk and thus controlled for in the selection of eligible patients. Standard least-squares regression was used to adjust the percent LDL-C change between the statins for patient characteristics. Logistic regression model coefficients were used to estimate the probability of attaining goal with different treatments, and the sample mean of predicted probabilities was used as an estimate of the expected rate of goal attainment by individual treatment adjusted for patient characteristics. All statistical analyses were conducted using SAS Version 9.1 (SAS Institute Inc, Cary, NC).

A decision model–based cost-effectiveness analysis was employed to estimate the incremental cost relative to incremental effectiveness between rosuvastatin and atorvastatin, as well as between rosuvastatin and simva-statin. The analysis employed the payer perspective with direct medical costs only and a time horizon of 1 year. Patient-level effectiveness parameters were taken from the multivariate regression models and included percentage reduction in LDL-C, achievement of ATP III goal, and achievement of the 2004 proposed goal. Resource-use parameters were based on actual utilization observed in the study cohort and included annualized statin costs and cost of titration. Routine physician visits and laboratory tests were not included because there was no anticipated difference in utilization among the statins.[22] Unit costs were based on Medicare reimbursement rates for physician visits associated with titration of the statin doses (measured as the average of the 2006 Medicare Physician Fee Schedule for 99212 and 99213, or $60).[23] Unit drug costs were based on the wholesale acquisition cost (WAC) of statins as of March 2006.[24] The base-case branded drug price was $2.63 for rosuvastatin (all doses); $2.31 and $3.30 for atorvastatin (10- and 20-mg and higher doses, respectively); and $1.87, $2.51, and $4.37 for simvastatin (5-, 10-, and 20-mg or higher doses, respectively).

All cost-effectiveness models were estimated using TreeAge Pro Healthcare (TreeAge Software, Inc, Williamson, Mass). Key parameters were subjected to extensive sensitivity analyses with particular attention to the drug cost inputs, given possible generic pricing of simvastatin in late 2006.[25,26] Dominance in the incremental cost-effectiveness analyses indicates that a drug treatment is more effective and less costly than an alternate drug treatment. Given that most payers employ tiered patient copayments for generic and brand drugs, different generic and brand patient copayments were assumed to estimate payer costs minus patient payments. Further, manufacturers of brand drugs usually provide a rebate, whereas generic drug manufacturers do not.

Thus, 4 different scenarios were analyzed that included an assumed rebate of 20% for branded statins (rosuvastatin and atorvastatin) plus variations on the percent discount from WAC for generic simvastatin and differential patient copayments for generic and brand drugs. The 4 scenarios were as follows: (1) 20% brand rebate, 60% discount off WAC for simvastatin, and $10 copay for generics and $25 copay for brand statins; (2) 20% brand rebate, 70% discount off simvastatin WAC price, and $10 generic and $25 brand copay; (3) 20% brand rebate, 60% discount off simvastatin WAC price, and $5 generic and $15 brand copay; and (4) 20% brand rebate, 70% discount off simvastatin WAC price, and $5 generic and $15 brand copay. Additionally, Monte Carlo simulation across all model parameters was conducted for the 2 extreme scenarios (scenarios 2 and 3). The simulations were based on 1000 simulated populations of 10 000 patients each. The Monte Carlo simulation identified situations in which a particular treatment provides acceptable cost-effectiveness based on the payer's willingness-to-pay threshold, as a key model parameter is varied (eg, drug acquisition costs).[25,26] Furthermore, a threshold analysis was performed for differ-

ent copayment levels for willingness-to-pay equal to $0 to determine the price point at which rosuvastatin is preferred over simvastatin using generic simvastatin pricing.[27]

Results

The eligible study population consisted of 775 patients; 63 taking rosuvastatin, 480 taking atorvastatin, and 232 taking simvastatin. Baseline characteristics of the population showed the average age as 61.0 ± 11.7 years and 52.4% male. Several characteristics differed among the patients taking statins. Rosuvastatin patients were younger and had a higher baseline LDL-C and total cholesterol levels than either atorvastatin or simvastatin patients (**Table 1**). Because the initial LDL-C level was higher for the rosuvastatin patients, these patients were further from attaining ATP III goals and required a greater LDL-C reduction than atorvastatin or simvastatin patients. The rosuvastatin patients also had a significantly shorter length of statin therapy (125.9 ± 84.9 days) than atorvastatin or simvastatin patients (260.6 ± 151.2 days and 264.2 ± 149.7 days, respectively). The majority of patients were taking 10-mg rosuvastatin (87%), 10-mg atorvastatin (68%), or 20-mg simvastatin (57%), indicating median doses. The mean starting dose of rosuvastatin was 10 mg, whereas the average dose for atorvastatin and simvastatin was 14 mg and 25 mg, respectively.

Change in Lipid Parameters. Rosuvastatin patients had the greatest observed decrease in LDL-C levels with an average –41.3% ± 19.5% reduction in LDL-C compared with –28.1% ± 25.6% for atorvastatin and –25.4% ± 25.4% for simvastatin patients (**Table 2**). Multivariate analyses adjusting for baseline differences in age, sex, presence of CHD, baseline LDL-C, and treatment duration also demonstrated that rosuvastatin patients had the greatest percentage decrease (–36.6%) in LDL-C levels that was statistically significantly larger (P <.05) than either atorvastatin or simvastatin (–28.0% or –26.7%, respectively) (Table 2).

Total cholesterol change among the statins was statistically significantly greater

Table 1. Baseline Characteristics of High-risk Patients Treated in Clinical Practice, by Statin Therapy Type

Characteristics	Rosuvastatin	Atorvastatin	Simvastatin
Number of subjects	63	480	232
Age, mean ± SD, y	58 ± 12*	61 ± 12	62 ± 11
Male, %	56	51	55
White, %	83	78	80
CHD, %	57	55	55
Diabetes, %	57	64	67
Hypertension, %	43*	68	72
Baseline lipid parameters			
LDL-C, mean ± SD, mg/dL	156.2 ± 34.3*	141.5 ± 38.9	136.7 ± 34.1
TC, mean ± SD, mg/dL	240.6 ± 30.1*	229.6 ± 47.0	223.3 ± 37.9
HDL-C, mean ± SD, mg/dL	46.8 ± 15.7	49.4 ± 25.9	47.9 ± 13.0
TG, mean ± SD, mg/dL	169.8 ± 62.7	177.9 ± 75.8	175.2 ± 74.0

*P <.05 for comparison with atorvastatin and simvastatin.
SD indicates standard deviation; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Table 2. Mean Percent Change in Lipid Parameters by Statin Type Among High-risk Patients

Lipid Parameter	Mean Percent Change		
	Rosuvastatin, Mean (SD)	Atorvastatin, Mean (SD)	Simvastatin, Mean (SD)
Number of subjects	63	480	232
LDL-C, %	–41.3 (19.5)	–28.1* (25.6)	–25.4* (25.4)
LDL-C, adjusted, %†	–36.6 (2.8)	–28.0* (1.0)	–26.7* (1.4)
TC, %	–30.5 (15.0)	–22.5* (17.2)	–19.8* (16.1)
TC, adjusted, %†	–29.0 (1.8)	–22.3* (0.6)	–20.6* (0.9)
HDL-C, %	+1.1 (23.3)	+2.7 (24.8)	+5.2 (20.1)
TG, %	–13.4 (34.9)	–17.7 (31.0)	–7.9 (53.6)

*P <.05 compared with rosuvastatin.
†Mean percent change adjusted for age, sex, presence of CHD, baseline LDL-C, and treatment duration.
SD indicates standard deviation; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CHD, coronary heart disease.

(P <.05) for rosuvastatin users (observed mean change: –30.5% ± 15.0%, adjusted mean change: –29.0% ± 1.8%) compared with atorvastatin or simvastatin (Table 2). There was no significant difference in the change in high-density lipoprotein cholesterol and triglycerides among the statins.

NCEP Goal Attainment. NCEP ATP III guidelines recommended a goal of LDL-C <100 mg/dL for high-risk patients and the 2004 update recommended an optional goal of LDL-C <70 mg/dL for very high-risk patients (ie, patients with cardiovascular disease and diabetes, acute coronary syndrome, or metabolic syndrome). After adjusting for differences in baseline characteristics, the odds of attaining NCEP ATP III and the updated ATP III goals were greatest with rosuvastatin users. Atorvastatin users were 50% less likely (odds ratio [OR] = 0.50, 95% confidence interval [CI]: 0.27-0.92) and simvastatin users were 57% less likely (OR = 0.43, 95% CI: 0.22-0.82) than rosuvastatin users to attain LDL-C <100 mg/dL (**Table 3**). Likewise, atorvastatin users had a 56% (OR = 0.44, 95% CI: 0.22-0.87) lower likelihood and simvastatin users had a 69% (OR = 0.31, 95% CI: 0.14-0.64) lower likelihood of attaining the goal than rosuvastatin users when optional updated goals were included in the goal attainment estimation.

Table 3. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Attaining LDL-C Goals*

Statin Therapy	OR (95% CI)	*P* Value
ATP III LDL-C goal†		
Atorvastatin (n = 425)	0.50 (0.27-0.92)	.024
Simvastatin (n = 201)	0.43 (0.22-0.82)	.009
ATP III and optional LDL-C goal†		
Atorvastatin (n = 425)	0.44 (0.22-0.87)	.016
Simvastatin (n = 201)	0.31 (0.14-0.64)	.001

*LDL-C goals: ATP III LDL-C goal among high-risk patients and optional updated LDL-C goal among high- and very high-risk patients.
†All comparisons are with rosuvastatin (n = 60) and adjusted for baseline differences in age, sex, baseline LDL-C, treatment duration, CHD, and very high-risk status.
LDL-C indicates low-density lipoprotein cholesterol; ATP III, Adult Treatment Panel III; CHD, coronary heart disease.

After adjusting for differences in baseline characteristics, the estimated percent of patients attaining the ATP III goal was significantly higher (P <.05) among rosuvastatin patients (69.7%) than among atorvastatin (54.8%) or simvastatin (51.2%) patients (**Table 4**). Likewise, the adjusted percent attaining ATP III and the optional LDL-C goal for very high-risk patients was significantly greater (P <.05) among rosuvastatin patients (58.1%) than among atorvastatin (43.4%) or simvastatin (36.9%) patients.

Cost-effectiveness. In the base-case analysis of drug costs (WAC pricing) and titration costs (physician visits), rosuvastatin had the lowest annualized cost ($962), followed by atorvastatin ($1048) and simvastatin ($1538). Adjusted for differences in patient characteristics, mean annualized costs were $934 for rosuvastatin, $1050 for atorvastatin, and $1545 for simvastatin. Using the adjusted LDL-C reduction and percent attaining goal (both ATP III and optional goal), rosuvastatin was the most cost-effective therapy among the high-risk patients with the lowest adjusted annualized cost per unit of LDL-C reduction ($25), the lowest cost per patient treated to ATP III LDL-C goal of <100 mg/dL ($1340), and the lowest cost per patient treated to the optional LDL-C goal ($1607). For incremental cost-effectiveness, rosuvastatin dominated (less costly and more effective) both atorvastatin and simvastatin for LDL-C reduction and both LDL-C goals (**Table 5**). Rosuvastatin dominated both atorvastatin and simvastatin on a cost-effectiveness basis (ie, treatment using rosuvastatin entailed lower cost than atorvastatin and simvastatin while also providing greater effectiveness).

Base-case results were most sensitive to the acquisition costs of rosuvastatin, atorvastatin, and simvastatin. Thus, particular focus was placed on the pricing of simvastatin (because generic simvastatin is now

Table 4. Adjusted Percentage of Patients Attaining LDL-C Goals*

Statin Therapy	ATP III LDL-C <100 mg/dL Goal	ATP III Optional LDL-C <100 mg/dL for High-risk and <70 mg/dL Goal for Very High-risk Patients
Rosuvastatin	69.7%† (n = 60)	58.1%† (n = 60)
Atorvastatin	54.8% (n = 425)	43.4% (n = 444)
Simvastatin	51.2% (n = 201)	36.9% (n = 207)

*LDL-C goals: ATP III LDL-C goal <100 mg/dL among high-risk patients and optional LDL-C goal <70 mg/dL among very high-risk patients, and <100 mg/dL for high-risk patients.
†$P < .05$.
LDL-C indicates low-density lipoprotein cholesterol; ATP III, Adult Treatment Panel III.

Table 5. Base-case Cost per Patient per LDL-C Reduction and Cost per Patient to Attain ATP III Goal or Updated Optional Goal

Therapy	Effectiveness, %	Annualized Cost, $	Cost-effectiveness Ratio (Cost per Unit of Effectiveness)	Incremental Cost-effectiveness Ratio
LDL-C Reduction (effectiveness as % LDL-C reduction)				
Rosuvastatin	36.7	934	25	—*
Atorvastatin	28.1	1050	37	Dominated†
Simvastatin	26.7	1545	58	Dominated
ATP III LDL-C Goal (effectiveness as % of patients at goal)				
Rosuvastatin	69.7	936	1343	—
Atorvastatin	54.8	1047	1911	Dominated
Simvastatin	51.2	1538	3025	Dominated
Updated LDL-C Goal (effectiveness as % of patients at goal)				
Rosuvastatin	58.1	937	1612	—
Atorvastatin	43.4	1047	2413	Dominated
Simvastatin	36.9	1550	4200	Dominated

*Lowest cost treatment is the reference treatment in incremental cost-effectiveness analysis.
†Dominated = less effective and more costly than alternative treatment.
LDL-C indicates low-density lipoprotein cholesterol; ATP III, Adult Treatment Panel III.

Table 6. LDL-C Reduction Sensitivity Analysis Scenarios for Generic Simvastatin with Rebates and Copayments

Therapy	Effectiveness, % (LDL-C Reduction)	Annualized Cost, $	Cost-effectiveness Ratio (Cost per % LDL-C Reduction)	Incremental Cost-effectiveness Ratio
Scenario 1: 20% brand rebate, 60% discount off simvastatin WAC price, $10 generic and $25 brand copayments				
Rosuvastatin	36.7	463	13	—*
Atorvastatin	28.1	550	20	Dominated†
Simvastatin	26.7	519	19	Dominated
Scenario 2: 20% brand rebate, 70% discount off simvastatin WAC price, $10 generic and $25 brand copayments				
Rosuvastatin	36.7	463	13	9
Atorvastatin	26.7	550	21	Dominated
Simvastatin	26.7	369	14	—
Scenario 3: 20% brand rebate, 60% discount off simvastatin WAC price, $5 generic and $15 brand copayments				
Rosuvastatin	36.7	579	16	—
Atorvastatin	28.1	669	24	Dominated
Simvastatin	26.7	580	22	Dominated
Scenario 4: 20% brand rebate, 70% discount off simvastatin WAC price, $5 generic and $15 brand copayments				
Rosuvastatin	36.7	579	16	21
Atorvastatin	26.7	670	25	Dominated
Simvastatin	26.7	369	14	—

*Lowest cost treatment is the reference treatment in incremental cost-effectiveness analysis.
†Dominated = less effective and more costly than alternative treatment.
LDL-C indicates low-density lipoprotein cholesterol; WAC, wholesale acquisition cost.

available), and on the impact of manufacturer rebates and differential copayment levels on net cost for payers. For LDL-C reduction, when simvastatin price was discounted by 60% and a 20% brand rebate applied, rosuvastatin dominated both atorvastatin and simvastatin for different copay levels ($10 generic/$25 brand for scenario 1 and $5 generic/$15 brand for scenario 3; **Table 6**). Thus, rosuvastatin was more effective and less costly than atorvastatin and simvastatin when a 20% brand rebate, different patient copays, and a 60% discount on simvastatin price were applied. If simvastatin price were discounted by 70% and the brand rebate and copayments were applied, rosuvastatin had an incremental cost-effectiveness ratio of $9 per 1% LDL-C reduction compared with simvastatin for scenario 2 and $21 for scenario 4 (Table 6). Similarly, the goal attainment sensitivity analyses showed that rosuvastatin dominated atorvastatin and simvastatin when simvastatin pricing was discounted by 60% and a 20% brand rebate and patient copayments were applied (**Table 7**; scenarios 1 and 3). When simvastatin was discounted by 70% with the brand rebate and copayments applied, simvastatin dominated based on lower price for less effectiveness than rosuvastatin (Table 7; scenarios 2 and 4). In all scenarios evaluated, rosuvastatin dominated atorvastatin. As of October 2006, the generic simvastatin price was $1.58, $2.12, and $3.69, respectively, for 5 mg, 10 mg, and 20 mg and higher. Based on the doses prescribed for the study patients, the average generic simvastatin price was $3.48, approximately a 16% discount from its branded WAC price ($4.12). Given this current generic price, rosuvastatin is more effective and less costly than generic simvastatin.

Sensitivity analyses with Monte Carlo simulation provided the cost-effectiveness acceptability landscape for each outcome of interest and included all 3 statins. For ATP III goal attainment, the likelihood that rosu-

Table 7. Goal Attainment Sensitivity Analysis Scenarios for Generic Simvastatin With Rebates and Copayments

Therapy	Effectiveness, %	Annualized Cost, $	Cost-effectiveness Ratio (Cost per Patient Attaining Goal)	Incremental Cost-effectiveness Ratio
ATP III goal attainment, % patients				
Scenario 1: 20% brand rebate, 60% discount off simvastatin WAC price, $10 generic and $25 brand copayments				
Rosuvastatin	69.7	461	661	—*
Atorvastatin	54.8	542	1059	Dominated†
Simvastatin	51.2	517	943	Dominated
Scenario 2: 20% brand rebate, 70% discount off simvastatin WAC price, $10 generic and $25 brand copayments				
Rosuvastatin	69.7	461	661	511
Atorvastatin	54.8	542	990	Dominated
Simvastatin	51.2	366	715	—
Scenario 3: 20% brand rebate, 60% discount off simvastatin WAC price, $5 generic and $15 brand copayments				
Rosuvastatin	69.7	577	827	—
Atorvastatin	54.8	662	1207	Dominated
Simvastatin	51.2	577	1128	Dominated
Scenario 4: 20% brand rebate, 70% discount off simvastatin WAC price, $5 generic and $15 brand copayments				
Rosuvastatin	69.7	577	827	1137
Atorvastatin	54.8	662	1207	Dominated
Simvastatin	51.2	366	715	—
Updated optional goal attainment, % patients				
Scenario 1: 20% brand rate, 60% discount off simvastatin WAC price, $10 generic and $25 brand copayments				
Rosuvastatin	58.1	463	796	—
Atorvastatin	43.4	543	1252	Dominated
Simvastatin	36.9	518	1404	Dominated
Scenario 2: 20% brand rebate, 70% discount off simvastatin WAC price, $10 generic and $25 brand copayments				
Rosuvastatin	58.1	463	796	449
Atorvastatin	43.4	543	1252	Dominated
Simvastatin	36.9	367	995	—
Scenario 3: 20% brand rebate, 60% discount off simvastatin WAC price, $5 generic and $15 brand copayments				
Rosuvastatin	58.1	578.40	996	—
Atorvastatin	43.4	663	1527	Dominated
Simvastatin	36.9	578.60	1568	Dominated
Scenario 4: 20% brand rebate, 70% discount off simvastatin WAC price, $5 generic and $15 brand copayments				
Rosuvastatin	58.1	578	996	996
Atorvastatin	43.4	663	1527	Dominated
Simvastatin	36.9	367	995	—

*Lowest cost treatment is the reference treatment in incremental cost-effectiveness analysis.
†Dominated = less effective and more costly than alternative treatment.
ATP III indicates Adult Treatment Panel III; WAC, wholesale acquisition cost.

vastatin was preferred over simvastatin was reached at a willingness-to-pay of $520 for each additional patient attaining LDL-C goal when simvastatin price was 70% less than current WAC and a 20% brand rebate and patient copay of $10 generic and $25 brand were applied. When simvastatin price was reduced to 60% of WAC and a 20% brand rebate and $5 generic and $15 brand copay were applied, the likelihood that rosuva-

Table 8. Threshold Generic Simvastatin Price as a Proportion of Current Branded Price for Different Patient Copayment Levels

	Threshold Generic Simvastatin Price Compared With Current WAC*		
Patient Copayment	LDL-C Reduction	ATP III LDL-C Goal†	Updated Optional Goal†
$5 Generic/$15 brand	0.401	0.396	0.398
$10 Generic/$25 brand	0.357	0.346	0.348
$10 Generic/$30 brand	0.321	0.307	0.308

*Generic simvastatin price threshold above which rosuvastatin is preferred at willingness-to-pay = $0. A rebate of 20% for branded statin manufacturers to payers is assumed.
†LDL-C goals: ATP III LDL-C goal <100 mg/dL among high-risk patients and optional LDL-C goal <70 mg/dL among very high-risk patients, and <100 mg/dL for high-risk patients.
WAC indicates wholesale acquisition cost; LDL-C, low-density lipoprotein cholesterol; ATP III, Adult Treatment Panel III.

statin was preferred over simvastatin was achieved at willingness-to-pay equal to $0.

The threshold analysis demonstrated that rosuvastatin dominated simvastatin at any generic price of simvastatin above the threshold of 30% to 40% of current WAC (**Table 8**). When the differential in patient copayment was the smallest ($5 generic/$15 brand), the threshold for generic simvastatin price was highest, approximately 40% of WAC. With a copayment differential of $15 between generic and brand, the threshold was approximately 35% of WAC. The threshold dropped to 31% to 32% when the copayment differential was $20.

Discussion

Rosuvastatin was more effective in lowering LDL-C (–36.7% change) and total cholesterol (–29.0% change) in high-risk patients. Rosuvastatin was more effective in getting patients to attain NCEP ATP III and the updated optional NCEP goals compared with atorvastatin and simvastatin. In addition, rosuvastatin provided greater treatment effectiveness at lower treatment costs than atorvastatin and simvastatin for high-risk patients in clinical practice in both LDL-C reduction and NCEP goal attainment. Thus, in base-case models, rosuvastatin dominated both atorvastatin and simvastatin as treatment strategies, because atorvastatin and simvastatin were less effective and more costly than rosuvastatin among patients treated in the community. The implications of these findings are important for managed care decision makers. Under the base-case analysis, atorvastatin and simvastatin were always dominated. Thus, payers may achieve substantial cost savings and greater effectiveness among high-risk patients by using rosuvastatin rather than atorvastatin or simvastatin, depending on the actual acquisition prices.

The sensitivity analyses tested the pricing range for simvastatin and atorvastatin versus rosuvastatin in addition to applying a rebate for branded statins and differential patient copayments. Managed care organizations (MCOs) are provided with rebates on branded drugs. Additionally, in health plans using pharmacy benefit designs with tiered copayments, the differential cost between branded rosuvastatin and generic simvastatin for the health plans would be further reduced by higher patient copays for a branded versus generic drug. As simvastatin transitions to a generic product, rebates will continue to be provided for rosuvastatin and atorvastatin and patient copayments will differ, closing the gap between the cost differential. Our findings confirm that rosuvastatin will continue to dominate simvastatin with a 60% discount off WAC, a 20% brand rebate, and a differential of $10 in patient copays. The threshold analysis also affirmed that rosuvastatin dominated simvastatin at all generic simvastatin pricing above 31% to 40% of current WAC for LDL-C reduction and goal attainment. Hence, the pricing of simvastatin would have to be discounted by at least 60% to achieve superior cost-effectiveness based on lower price with less effectiveness than rosuvastatin. Even if this simvastatin discount was achieved, individual patient needs (in terms of the extent of LDL-C reduction desired) would need to be considered for selecting generic simvastatin or the more effective rosuvastatin.

It is important for MCOs to have as many patients as possible achieve NCEP goals, because several quality-of-care initiatives are based on these goals. The National Committee for Quality Assurance Health Plan

Employer Data and Information Set establishes benchmarks for quality of care provided by MCOs for patients after an acute cardiovascular event based on the proportion of patients achieving NCEP goals.[28] Additionally, several pay-for-performance programs[29,30] are currently in place to reward physicians who intensively treat their patients and get them to the NCEP target goals.

This study is unique because it is based on actual clinical practice. The LDL-C reduction and NCEP goal attainment were the outcomes observed among patients from different physician offices on their usual care regimen rather than patients selected and randomized in a clinical trial. Other investigations have quantified the efficacy[3,5,31] and cost-effectiveness[22,32] of statin therapy from clinical trial data that included a select group of patients. The results from our study are similar to those investigations using clinical trial data. Rosuvastatin was shown to be the most efficacious statin,[33] and we found rosuvastatin to be the most effective of the 3 high-efficacy statins in clinical practice. Similar to our findings, Benner and colleagues[22] found rosuvastatin to be the most cost-effective statin and dominated atorvastatin, pravastatin, and simvastatin under the base-case and several alternative scenarios using data derived from clinical trials.

Moreover, this study uniquely focused on those high-risk patients who have been diagnosed with CHD and required intensive lipid-lowering therapy according to the NCEP ATP III guidelines. Other investigators have examined either the overall effectiveness of statin therapy or effectiveness in different patient populations at various risk levels depending on the clinical trial population or the composition of their health plan.[34-37] Similar to our findings, several recent investigations have shown that rosuvastatin was more effective in LDL-C reduction than other statins.[38,39] Bullano and colleagues showed that a greater percent of patients reached NCEP ATP III LDL-C goal with rosuvastatin compared with all other statins for high- and moderate-risk patients.[40] Our study confirmed this greater effectiveness of rosuvastatin for LDL-C reduction and goal attainment compared with atorvastatin and simvastatin among the high-risk patients who require intensive lipid-lowering therapy. Recent evidence has confirmed the clinical benefits of aggressive lipid lowering, particularly in patients with an elevated risk for CHD.[41,42]

The study findings should be interpreted in light of several limitations. The patients are from physician practices in the Midwest, and the treatment patterns observed in this group of patients may not be representative of clinical practice in other areas of the United States. However, our findings are similar to other reported studies of patients in Western and Southeastern health plans.[38-40] Costs were estimated using published WAC for drugs and Medicare reimbursement rates for physician visits for drug titration. These costs may not reflect the actual costs negotiated by MCOs, but wide variations in these parameters were tested to find relevant thresholds that changed rosuvastatin dominance. Costs associated with laboratory procedures, adverse drug events, and routine physician visits were excluded, but these costs were not expected to differ across treatment groups and therefore would not have affected the incremental cost-effectiveness analysis.

The duration of statin therapy was limited to ≤18 months because rosuvastatin was new to the market and patients did not have the opportunity to receive rosuvastatin for as long as atorvastatin and simvastatin. However, therapy duration was still shorter for rosuvastatin patients compared with those taking the other statins (126 vs 261-264 days, respectively). Controlling for therapy duration did not impact the results for LDL-C reduction or goal attainment. The analysis had a 1-year time horizon and thus examined short-term end points (LDL-C reduction and ATP III goal attainment) instead of long-term outcomes, such as cost per life-year gained or cost per avoided CHD event. A longer follow-up period or analytic model would be required to estimate the long-term outcomes.

Fewer patients were taking rosuvastatin than atorvastatin or simvastatin. This was expected, because the study period included market introduction of rosuvastatin and

thus less use of rosuvastatin compared with atorvastatin or simvastatin in clinical practice. Future studies with more robust sample sizes could be used to confirm the present study results. Also, the study did not allow for switching and therefore may have selected patients without any tolerability issues with the individual statins. Our analyses applied the optional LDL-C goal of <70 mg/dL for all very high-risk patients even though the goal was not recommended until 2004. Therefore, considering this limitation, our findings with regard to attaining the optional LDL-C goals should be interpreted with caution.

In conclusion, the findings indicated that managing hyperlipidemia patients with rosuvastatin is more effective and less costly than with atorvastatin or generic simvastatin (at current prices). Moreover, a substantial discount from the current branded price would be needed for generic simvastatin to be equally as cost-effective as rosuvastatin for payers. These findings reflect treatment effectiveness as observed in clinical practice for patients treated with statin therapy rather than the efficacy demonstrated for doses used in clinical trials.

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