doi: 10.1111/j.1742-1241.2007.01538.x

ORIGINAL PAPER

International Journal of Clinical Practice

Effectiveness of statins in Medicare-eligible patients and patients < 65 years using clinical practice data*

K. M. Fox,[1] S. K. Gandhi,[2] R. L. Ohsfeldt,[3] J. W. Blasetto,[4] M. H. Davidson[5]

[1]Department of Epidemiology & Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, USA
[2]Health Economics and Outcomes Research, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA
[3]Department of Health Policy and Management, Texas A&M Health Science Center, College Station, TX, USA
[4]Clinical Development, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA
[5]Radiant Research, Chicago, IL, USA

Correspondence to:
Kathleen M. Fox,
PO Box 543, Monkton,
MD 21111, USA
Tel.: + 443 690 2198
Fax: + 410 357 8018
Email:
kathyfox@comcast.net

Disclosures
This research was funded by AstraZeneca Pharmaceuticals LP. Dr Fox is a paid consultant for AstraZeneca LP, Dr Gandhi and Dr Blasetto are employees of AstraZeneca LP, Dr Ohsfeldt has no competing interest and Dr Davidson is an advisory board member for AstraZeneca LP.

*A subset of the study results were presented as a poster at the American Heart Association 7th Scientific Forum on Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke, May 2006.

SUMMARY

Objective: This study compared effectiveness of rosuvastatin (RSV) with other statins on lowering LDL-C and LDL-C goal attainment among Medicare-eligible patients (age ≥ 65 years) and patients with age < 65 years treated in usual clinical practice to provide evidence of real-world effectiveness of statins. **Methods:** Retrospective cohort study was conducted in patients, newly prescribed statin therapy during August 2003 to May 2005. Patient inclusion criteria: no prior prescription for dyslipidaemic medication in the preceding 12 months, continuously enrolled for ≥ 15 months and ≥ 90-day supply of statin. Effectiveness of RSV in reducing LDL-C and attaining LDL-C goal when compared with other statins was evaluated using multivariate regression, adjusting for baseline LDL-C, age, gender, smoking, hypertension, coronary heart disease (CHD), systolic blood pressure and therapy duration. **Results:** Adjusted per cent LDL-C reduction was significantly greater ($p < 0.05$) with RSV (24.3% for ≥ 65 and 28.5% for < 65) compared with ATV (17.5%, 21.3%), SMV (14.8%, 18.4%), PRV (11.3%, 15.8%), FLV (10.7%, 20.6%) and LOV (13.3%, 14.4%). Among patients in both age groups at high or moderate CHD risk, a greater proportion of RSV patients attained LDL-C goal (76.0% for age group ≥ 65 years and 78.4% for age group < 65 years) vs. 50.5–73.0% for ≥ 65 and 51.3–71.5% for < 65 years of age on other statins ($p < 0.0001$). **Conclusions:** Rosuvastatin is more effective in lowering LDL-C in Medicare-eligible patients and patients < 65 years of age when compared with other statins in usual clinical practice. Moreover, RSV patients had higher LDL-C goal attainment rates when compared with other statins in high- and moderate-risk patients. The study results have implications for clinicians in selecting the optimal statin to meet individual patient care needs.

What's known
Clinical trials have shown that statins are efficacious in managing dyslipidaemia and that rosuvastatin is more efficacious than other statins in lowering LDL-C. There have been only a few studies that examined the effectiveness of statins in clinical practice, outside the controlled trial setting. Most of these studies have not included rosuvastatin as it was introduced to the market later.

What's new
This investigation provides estimates of LDL-C lowering and LDL-C goal attainment among patients ≥ 65 years of age which has not been a focal point of other studies. Previous investigations have largely included patients < 65 years of age because of the lack of available databases with lipid results or have not stratified LDL-C by age group. Moreover, this study compared all marketed statins instead of a selected few statins.

Introduction

Management of patients with hyperlipidaemia remains an important healthcare issue as coronary heart disease (CHD) continues to be the leading cause of mortality and morbidity in the United States (US) affecting 13 million Americans and costing $130 billion annually (1). The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines highlighted the importance of aggressive hyperlipidaemia treatment by recommending LDL-C goal < 100 mg/dl for high-risk patients (2). In July 2004, an optional LDL-C goal < 70 mg/dl for very high-risk patients was recommended (3).

Investigations of patients treated with statins by community-based physicians are limited and indicate that treatment for hyperlipidaemia may be suboptimal (4–6) compared with clinical trial efficacy data (7–11). Reports indicate that many patients are not managed aggressively to reach ATP III goals, only 38–48% of patients in different health plans achieved goal (12,13) while only 23–24% of high-risk patients reached goal (14,15). With this gap in goal attainment, there is a need to determine if one statin is more effective than others in reducing LDL-C and attaining LDL-C goal so that physicians may optimise their patient outcomes.

Moreover, with the advent of Medicare D pharmacy benefits, older patients will potentially have greater access to statin therapy. Thus, clinicians need evidence regarding which statin is more effective for their Medicare-eligible patients (age ≥ 65 years) and patients < 65 years of age. This study was designed

to determine the differential effectiveness of rosuvastatin (RSV) compared with other statins in reducing LDL-C and reaching ATP III LDL-C goal among Medicare-eligible patients and patients < 65 years of age treated by physicians in usual clinical practice. This study provides evidence of how effective statins are in routine clinical practice and whether the effectiveness is similar for younger vs. older patients.

Methods

A retrospective cohort study was conducted utilising the General Electric Medical System (GEMS) electronic medical records database of patients treated in physician practices. The study objective was to examine the effectiveness of statins under usual care at reducing LDL-C and ATP III goal attainment by comparing RSV with atorvastatin (ATV), simvastatin (SMV), pravastatin (PRV), fluvastatin (FLV) and lovastatin (LOV). Older patients, 65 years and older, were examined separately from patients < 65 years of age to identify the most effective statin for the Medicare and non-Medicare population.

Patients who were newly prescribed statin therapy during August 2003 to May 2005 and had no prior prescription for dyslipidaemic medication, including bile acid sequestrants, fibrin, niacin, ezetimibe or statin, in the preceding 12 months were included in the study. The GEMS database included the electronic medical records (EMR) of patients treated in usual clinical practice for over 3000 physicians across the US. The EMR was utilised largely by primary care physicians (85%) and cardiology practices (~5%). All patient care activities (outpatient medical and procedures, prescriptions, laboratory) in the physician's office are captured in the EMR.

Titration of statin therapy was allowed but patients switching to other statins during the study period were excluded as the effect of the initial statin could not be isolated in patients switching statins. Patients had to be continuously enrolled for a minimum of 15 months; 12 months prior to and 3 months after initiation of statin therapy. Additionally, patients were required to have a minimum of 90-day supply of statin therapy (either a 90-day prescription or three 30-day prescriptions), and lipid results within 90 days prior to and > 30 days after initiating statin therapy. The lipid value closest to the date of statin therapy initiation was defined as the baseline lipid measure. The follow-up lipid value was defined as the average of all lipid measures during the follow-up period, from 30 days after initiation of statin therapy to the date of the last statin prescription at the time of discontinuation or end of study (August 2005). The average LDL-C was used to obtain stable estimates using all available data and followed the methodology by Bullano et al. (16). Therapy discontinuation was defined as the lack of a prescription or refill order within a 50% time period of the prescription supply. Thus, if a 30-day statin supply was ordered then the prescription must be refilled or a new order written within 45 days of the initial prescription to consider the patient persistent on statin therapy. Similarly, if a 90-day statin supply is ordered then the second prescription or refill must be written within 135 days of the initial prescription date to consider the patient persistent.

Two effectiveness outcomes were assessed: (1) per cent reduction in LDL-C and (2) percentage of patients attaining NCEP ATP III LDL-C goal. The outcome measures were computed for each individual statin and then compared with RSV. Change in total cholesterol, high-density lipoprotein (HDL-C) and triglycerides was also computed. For LDL-C goal attainment assessment, patients were stratified based upon NCEP CHD risk groups (2). CHD and CHD risk equivalent was defined as myocardial infarction, ischaemic heart disease, acute coronary syndrome, cerebral vascular accident, transient ischaemic attack, peripheral vascular disease, abdominal aortic aneurysm, angina pectoris, atherosclerosis and diabetes mellitus based on ICD-9 codes. The GEMS EMR (outpatient data only) did not contain information on inpatient procedures so the classification of patients with coronary artery bypass graft, angioplasty or other revascularisation into the high-risk category was not possible. A count of risk factors was done to assign patients to moderate or low risk. Moderate-risk patients were defined by the presence of two or more CHD risk factors including current cigarette smoking, hypertension diagnosis or blood pressure ≥ 140/90 mmHg, low HDL-C < 40 mg/dl and age ≥ 45 for men and ≥ 55 for women. Low-risk patients were those with one or no CHD risk factors.

Given the lack of inpatient procedures data and data from non-primary care settings, there was a potential for misclassifying high-risk patients as moderate risk. The fact that physicians started these patients with LDL-C < 130 mg/dl on a statin treatment was considered a strong indicator of their underlying high-risk status or a more aggressive LDL-C target goal (< 100 mg/dl). LDL-C goal was defined as < 100 mg/dl for high-risk patients as well as those moderate-risk patients who were already at goal < 130 mg/dl at baseline. Moderate-risk patients not at LDL-C goal at baseline had a goal of < 130 mg/dl (2). Low-risk patients' LDL-C goal was < 160 mg/dl (2). Moreover, family history of premature CHD was not available in the EMR and was not included as one of the risk factors. Thus, some

patients may have been classified as low risk instead of moderate risk.

Linear regression analyses were conducted to compare effectiveness of RSV with other statins in lowering LDL-C while adjusting for age, gender, smoking, hypertension, CHD, systolic blood pressure, baseline LDL-C and therapy duration. Logistic regression analyses were undertaken to compare LDL-C goal attainment between RSV and other statins while adjusting for the same baseline characteristics. The goal attainment analyses were stratified by CHD risk level, high plus moderate risk and low risk. The sample mean of predicted probabilities from the logistic regression models was used as an estimate of the expected rate of goal attainment adjusted for patient characteristics. All statistical analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Results

There were 5989 patients with age ≥ 65 years, and 5326 patients who were < 65 years of age who met the study inclusion criteria. RSV patients comprised 4% of the ≥ 65 age group and 6% of the < 65 age group (Table 1). RSV Medicare-eligible patients (age ≥ 65 years) and patients < 65 years of age had higher baseline LDL-C ($p < 0.05$) and total cholesterol ($p < 0.05$) than other statin patients except for LOV (Table 1). RSV patients also had shorter therapy duration ($p < 0.05$) than all other statin patients likely because of relatively recent availability when compared with other statins. Medicare-eligible RSV patients were younger than other statin patients ($p < 0.05$) except for ATV and SMV (Table 1). For patients < 65 years of age, RSV patients were significantly younger than SMV and LOV patients (Table 1). For both Medicare-eligible and patients < 65 years of age, initial statin dose did not vary by CHD risk level (Table 1).

Lipid changes

Medicare-eligible RSV patients had significantly greater ($p < 0.05$) LDL-C reduction (29.8%) compared with other statins (11.3–19.1%), despite differences in age and therapy duration (Table 2). For patients < 65 years of age, RSV patients had significantly greater ($p < 0.05$) observed LDL-C reduction (33.6%) compared with other statins (17–23.6%) (Table 2). After adjustment for differences in baseline characteristics, both Medicare-eligible patients and patients < 65 years of age, RSV patients had significantly greater LDL-C reduction than other statins ($p < 0.05$) (Table 2). After adjustment, patients < 65 years of age who were treated with RSV had a 28.5% LDL-C reduction compared with 14.4–21.3% for other statins. Similarly, Medicare-eligible RSV patients had a greater adjusted (24.3%) per cent LDL-C reduction compared with other statins (10.7–17.5%).

Medicare-eligible patients and patients < 65 years of age treated with RSV had significantly greater reduction in total cholesterol than other statin patients (Table 3). Medicare-eligible RSV patients had an adjusted 17.5% reduction in total cholesterol compared with 7.0–12.2% for other statins, $p < 0.05$. Among patients < 65 years of age, RSV had an adjusted 22.1% total cholesterol reduction compared with 17.2% for ATV ($p \geq 0.05$) and 10.8–14.1% for other statins ($p < 0.05$). The average change in HDL-C for each statin was 0.8–3.4% for Medicare-eligible and −1.3% to 1.7% for < 65 patients (Table 3). There was no difference in the change in triglycerides between RSV and other statins for either the Medicare-eligible patients or patients < 65 years of age.

ATP III goal attainment

ATP III goal attainment was computed by CHD risk level and patients who were at LDL-C goal level at baseline were excluded. A greater proportion of moderate- and high-risk RSV patients compared with other moderate- and high-risk statin patients, both Medicare-eligible patients and < 65, attained ATP III LDL-C goal after adjusting for baseline differences (Table 4). After adjustment, approximately 78% of < 65 years of age moderate- and high-risk patients and 76% of high- and moderate-risk Medicare-eligible patients attained LDL-C goal on RSV compared with 51–71% of < 65 years of age patients and 50–73% of older patients taking other statins (Table 4).

There was little difference across statins in LDL-C goal attainment among the low-risk patients for both Medicare-eligible patients and patients < 65 years of age (Table 4). After adjustment, a significantly greater proportion of low-risk RSV patients < 65 years of age had attained LDL-C goal compared with PRV and LOV ($p < 0.05$). For Medicare-eligible low-risk patients, a significantly greater proportion of RSV patients attained LDL-C goal than PRV ($p < 0.05$) after adjustment for baseline covariates.

Discussion

Rosuvastatin is more effective in lowering LDL-C in this sample of Medicare-eligible patients and patients < 65 years of age than other statins. These greater LDL-C reductions resulted in better goal attainment among RSV patients, both < 65 and

Table 1 Baseline characteristics of Medicare-eligible patients and < 65 years of age patients newly initiated on statin therapy

Characteristics	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	Lovastatin
Medicare-eligible patients (≥ 65 years) ($n = 5989$)						
Number of subjects	235 (4%)	3195 (54%)	1432 (24%)	495 (8%)	256 (4%)	376 (6%)
Age (mean ± SD)	73.3 (5.1)	73.5 (5.0)	74.0 (4.9)	74.1 (5.0)*	74.9 (5.0)*	74.5 (5.0)*
Male (%)	42	44	49	46	42	38
Smoker (%)	7	5	5	4	2	4
Hypertension (%)	55	52	50	53	50	56
CHD (%)	13	14	14	12	12	12
NCEP risk group, *n* (%)						
CHD/CHD risk equivalent†	96 (41%)	1557 (49%)	703 (49%)	216 (44%)	124 (48%)	146 (39%)
Mean statin dose	11.1	17.9	24.1	34.8	60.8	24.2
Moderate risk	78 (33%)	728 (23%)	301 (21%)	124 (25%)	61 (24%)	123 (33%)
Mean statin dose	13.3	17.8	23.1	34.8	61.3	24.3
Low risk	61 (26%)	910 (28%)	428 (30%)	155 (31%)	71 (28%)	107 (28%)
Mean statin dose	10.7	16.9	23.8	33.9	63.9	24.7
Baseline lipids, mean ± SD						
LDL-C	143.5 (47.0)	124.4 (43.5)*	118.9 (39.7)*	127.8 (39.7)*	126.8 (35.6)*	139.3 (38.6)
Total cholesterol‡	217.8 (47.9)	202.0 (44.6)*	195.5 (41.6)*	204.1 (39.4)*	206.8 (42.2)*	220.5 (40.6)
HDL-C‡	52.1 (14.9)	52.8 (13.9)	52.8 (14.4)	52.7 (13.9)	53.3 (15.1)	55.0 (14.3)
Triglycerides‡	148.1 (79.6)	144.8 (75.6)	140.1 (75.5)	138.9 (67.3)	146.9 (74.9)	145.3 (79.4)
Statin therapy, mean (SD)						
Initial daily dose	12.2 (7.2)	17.5 (12.9)	23.5 (11.5)	34.5 (14.7)	62.0 (24.8)	24.4 (11.0)
Therapy duration§, days	199.5 (123.0)	265.8 (160.4)*	266.1 (161.0)*	263.5 (158.6)*	287.0 (165.3)*	251.1 (158.9)*
< 65 years of age patients ($n = 5326$)						
Number of subjects	353 (6%)	3340 (63%)	944 (18%)	322 (6%)	143 (3%)	224 (4%)
Age (mean ± SD)	53.9 (7.7)	53.8 (7.9)	54.9 (7.4)*	54.9 (7.3)	55.0 (7.6)	55.2 (7.2)*
Male (%)	46	52	52	50	50	47
Smoker (%)	9	10	9	12	12	9
Hypertension (%)	42	37	40	39	36	46
CHD (%)	9	9	8	9	6	9
NCEP risk group, *n* (%)						
CHD/CHD risk equivalent†	78 (22%)	969 (29%)	264 (28%)	91 (28%)	31 (22%)	45 (20%)
Mean statin dose	10.5	19.6	24.9	31.8	51.4	24.1
Moderate risks	123 (35%)	735 (22%)	208 (22%)	77 (24%)	36 (25%)	67 (30%)
Mean statin dose	11.9	17.2	24.5	37.5	65.3	23.0
Low risk	152 (43%)	1636 (49%)	472 (50%)	154 (48%)	76 (53%)	112 (50%)
Mean statin dose	10.6	16.2	24.3	33.6	74.4	24.0
Baseline lipids, mean ± SD						
LDL-C	163.5 (48.1)	142.2 (46.4)*	140.3 (46.2)*	142.2 (38.4)*	147.9 (37.5)*	153.8 (40.6)*
Total cholesterol‡	239.8 (43.7)	219.1 (46.1)*	216.6 (44.7)*	218.4 (36.9)*	226.9 (32.2)*	230.5 (41.8)*
HDL-C‡	48.8 (12.7)	50.1 (13.0)	51.4 (13.5)	50.3 (12.5)	53.3 (13.5)	51.0 (14.6)
Triglycerides‡	179.6 (99.5)	160.2 (89.2)	156.5 (86.0)	155.8 (80.1)	145.7 (75.7)	157.3 (81.9)
Statin therapy, mean ± SD						
Daily dose	11.3 ± 5.3	16.5 ± 12.0	24.3 ± 11.3	35.7 ± 15.0	66.4 ± 21.7	23.5 ± 11.7
Therapy duration§, days	196.7 (121.0)	264.5 (159.4)*	266.0 (158.2)*	288.5 (159.6)*	276.0 (158.8)*	248.9 (153.1)*

*$p < 0.05$ for comparison with rosuvastatin; †CHD risk = high risk + moderate risk with baseline LDL-C < 130 mg/dl; ‡Number of subjects for total cholesterol, HDL-C and triglycerides were slightly less than that of LDL-C; Medicare-eligible, $n = 207$ for RSV, 2714 for ATV, 1201 for SMV, 452 for PRV, 219 for FLV and 350 for LOV; < 65 years of age, $n = 303$ for RSV, 2873 for ATV, 853 for SMV, 298 for PRV, 135 for FLV and 215 for LOV; §Therapy duration was shorter for RSV because of its more recent commercial availability compared with other statins.

≥ 65 age groups. For moderate- and high-risk RSV patients, 76% attained ATP III LDL-C goals compared with 50–73% of other statin patients. There was no difference in goal attainment across statins for low-risk patients. RSV was also more effective ($p < 0.05$) in lowering total cholesterol among Medicare-eligible patients and patients < 65 years of age than other statins.

Table 2 Observed changes in LDL-C levels for Medicare-eligible patients and < 65 years of age patients newly initiated on statin therapy

LDL-C	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	Lovastatin
< 65 years of age patients						
Number of subjects	353	3340	944	322	143	224
Baseline (mg/dl)	163.5 ± 48.1	142.2 ± 46.4*	140.3 ± 46.2*	142.2 ± 38.4*	147.9 ± 37.5*	153.8 ± 40.6*
Follow-up (mg/dl)	102.3 ± 36.6	102.1 ± 31.2	106.7 ± 31.4*	113.6 ± 27.6*	109.4 ± 27.1*	118.8 ± 31.5*
Per cent change (%)	33.6 ± 27.9	22.5 ± 29.4*	19.0 ± 25.6*	17.0 ± 20.2*	23.6 ± 20.1*	20.2 ± 19.9*
Adjusted per cent change† (%)	28.5 ± 15.7	21.3 ± 15.7*	18.4 ± 15.7*	15.8 ± 15.7*	20.6 ± 15.7*	14.4 ± 15.7*
Medicare-eligible patients						
Number of subjects	235	3195	1432	495	256	376
Baseline (mg/dl)	143.5 ± 47.0	124.4 ± 43.5*	118.9 ± 39.7*	127.8 ± 39.7*	126.8 ± 35.6*	139.3 ± 38.6
Follow-up (mg/dl)	93.8 ± 32.3	95.4 ± 28.6	97.4 ± 29.3	107.3 ± 32.8*	108.0 ± 30.5*	107.9 ± 27.3*
Per cent change (%)	29.8 ± 26.6	17.2 ± 28.8*	12.3 ± 33.0*	12.5 ± 23.7*	11.3 ± 25.1*	19.1 ± 22.0*
Adjusted per cent change† (%)	24.3 ± 16.6	17.5 ± 16.6*	14.8 ± 16.6*	11.3 ± 16.6*	10.7 ± 16.6*	13.3 ± 16.6*

*$p < 0.05$ for comparison of rosuvastatin vs. each other statin; †Adjusted for age, gender, smoking, hypertension, CHD, systolic blood pressure, therapy duration and baseline LDL-C.

Table 3 Per cent change in total cholesterol, HDL-C and triglycerides for Medicare-eligible patients and < 65 years of age patients newly initiated on statin therapy

Lipid change	Rosuvastatin	Atorvastatin	Simvastatin	Pravastatin	Fluvastatin	Lovastatin
< 65 years of age patients						
Total cholesterol						
Number of patients	303	2873	853	298	135	215
Per cent total cholesterol change	−23.6 (19.9)	−17.0 (18.2)*	−13.6 (16.7)*	−12.0 (13.3)*	−16.3 (13.6)*	−15.0 (13.7)*
Per cent total cholesterol change adjusted†	−22.1 (13.9)	−17.2 (13.9)	−14.1 (13.9)*	−10.8 (13.9)*	−16.0 (13.9)*	−13.6 (13.9)*
HDL-C						
Number of patients	303	2770	822	292	134	203
Per cent HDL-C change	1.7 (15.8)	0.8 (14.5)	1.2 (14.2)	−0.7 (13.8)*	0.6 (13.2)	−1.3 (11.9)*
Triglyceride						
Number of patients	301	2764	821	294	135	205
Per cent triglyceride change	−2.9 (62.5)	−4.5 (45.5)	−2.6 (39.3)	2.8 (40.2)	−2.1 (33.7)	−4.8 (30.8)
Medicare-eligible patients						
Total cholesterol						
Number of patients	207	2714	1201	452	219	350
Per cent total cholesterol change	−19.3 (18.6)	−12.3 (18.6)*	−8.9 (17.2)*	−9.3 (14.1)*	−7.9 (16.4)*	−13.2 (14.8)*
Per cent total cholesterol change adjusted†	−17.5 (10.6)	−12.2 (10.6)*	−10.7 (10.6)*	−8.8 (10.6)*	−7.0 (10.6)*	−8.8 (10.6)*
HDL-C						
Number of patients	206	2696	1203	450	217	347
Per cent HDL-C change	3.4 (14.6)	1.2 (15.0)*	1.7 (14.6)	1.6 (18.8)	1.8 (15.3)	0.8 (13.0)*
Triglyceride						
Number of patients	204	2698	1202	450	219	346
Per cent triglyceride change	15.7 (142.3)	2.0 (64.2)	9.8 (100.2)	5.4 (61.2)	5.0 (50.5)	4.9 (65.2)

*$p < 0.05$ for comparison of rosuvastatin vs. each other statin; †Adjusted for age, gender, smoking, hypertension, CHD, systolic blood pressure, therapy duration and baseline LDL-C.

A 6% difference in per cent LDL-C is considered to be clinically meaningful (17,18). A greater than 6% difference in LDL-C reduction between RSV and other statins as observed in the present study indicated clinical meaningfulness of the study findings. A definition for clinically meaningful difference in LDL-C goal attainment has not been established, so clinicians and payers may need to define their own clinically significant threshold. However, one could hypothesise that the clinically and statistically

Table 4 ATP III LDL-C goal attainment for rosuvastatin vs. other statins for Medicare-eligible patients and < 65 years of age patients by CHD risk group

	< 65 years of age			Medicare-eligible		
Statin therapy	**Number of subjects**	**Unadjusted percentage attaining LDL-C goal**	**Adjusted percentage attaining LDL-C goal†**	**Number of subjects**	**Unadjusted percentage attaining LDL-C goal**	**Adjusted percentage attaining LDL-C goal†**
Moderate- and high-CHD risk						
Rosuvastatin	187	73.6 (44.2)	78.4 (8.6)	136	74.1 (43.9)	76.0 (7.1)
Atorvastatin	1407	70.4 (45.6)	71.5 (9.4)*	1526	70.2 (45.7)	73.0 (7.5)*
Simvastatin	381	66.3 (47.3)	66.9 (10.3)*	623	62.0 (48.6)*	64.1 (8.6)*
Pravastatin	133	55.6 (49.8)*	59.7 (11.5)*	228	57.6 (49.5)*	59.5 (8.9)*
Fluvastatin	57	63.2 (48.6)	65.8 (10.9)*	118	48.6 (50.2)*	50.5 (9.0)*
Lovastatin	109	55.0 (50.0)*	51.3 (11.5)*	213	62.4 (48.5)*	64.8 (8.5)*
Low CHD risk						
Rosuvastatin	90	90.0 (30.2)	91.0 (7.7)	24	89.5 (31.5)	85.4 (11.0)
Atorvastatin	713	90.2 (29.7)	91.0 (7.6)	205	91.3 (28.3)	85.7 (10.9)
Simvastatin	179	89.5 (30.7)	90.1 (7.7)	72	90.0 (30.2)	83.0 (12.1)
Pravastatin	58	83.6 (37.3)	82.6 (12.0)*	27	82.8 (38.4)	74.7 (14.9)*
Fluvastatin	28	92.6 (26.7)	91.0 (7.1)	8	81.8 (40.4)	72.2 (15.5)
Lovastatin	54	80.4 (40.1)*	82.5 (12.0)*	41	94.3 (23.5)	88.8 (9.2)

*$p < 0.05$ for comparison of rosuvastatin vs. each other statin; †Adjusted for per cent LDL-C reduction needed to reach goal, age, gender, smoking, hypertension, CHD, systolic blood pressure and therapy duration.

meaningful difference in LDL-C reduction as observed in this study should equate to a clinically meaningful difference in goal attainment.

The present study only focused on lipid changes and goal attainment comparisons of RSV with other statins and did not examine mortality or cardiovascular event differences as end-points. Clinical trials examining the impact of RSV on mortality and cardiovascular event outcomes are ongoing (19–21). A meta analysis of 14 randomised trials of statin therapy indicated that statins safely reduced the 5-year incidence of major coronary events, coronary revascularisation and stroke by about one-fifth per mmol/l (39 mg/dl) reduction in LDL-C (22). This analysis found an approximately linear relationship between the absolute reductions in LDL-C achieved and the proportional reductions in the incidence of coronary and other major vascular events and that larger LDL-C reductions produced larger reductions in vascular disease risk. These results cannot be directly applied to the current study findings as it is not a randomised trial and there are obvious differences in inclusion criteria and follow-up period between the trials included in the meta analysis when compared with the current observational study. However, one can use the results of the meta analysis to arrive at a general guidance of the expected benefits in terms of avoided cardiovascular events. Extrapolating to the study's 49.7 mg/dl average absolute reduction in LDL-C for Medicare-eligible patients and 61.2 mg/dl average absolute reduction in LDL-C for < 65 years of age patients with RSV, it could be estimated that continued RSV therapy could reduce major vascular events by one-fourth and one-third respectively. Such estimates can also be projected for other statins in this study or for differences in LDL-C reduction observed between different statins.

This study provides evidence of greater effectiveness of RSV in usual care. The data reflect patients treated in the community, largely by primary care physicians, and represent clinicians' treatment patterns for their statin patients. Moreover, this is the first investigation to provide effectiveness estimates of statins for the Medicare-eligible population. Other studies have derived estimates from clinical trial populations and managed care populations which tend to be predominantly younger and employed rather than ≥ 65 and retired. It is also important to recognise that many patients on statin therapy (both Medicare-eligible and < 65 years) were not achieving their LDL-C goal in usual care. As few as 51–65% of patients reached goal on LOV, PRV or FLV, leaving 34–49% of patients not attaining LDL-C goal. Thus, the selection of a statin that increases the likelihood of attaining goal is important. Future studies need to examine specific reasons for this low LDL-C goal attainment rate and limited adoption of guidelines.

Statin therapy utilisation patterns were different between patients with ≥ 65 and < 65 years of age, with more Medicare-eligible patients receiving

generic statins (38%) than < 65 years of age patients (28%). Additionally, age ≥ 65 was an independent predictor of LDL-C outcomes in the total population. Hence, we examined statin effectiveness in the age-stratified groups of < 65 and ≥ 65.

Our effectiveness estimates were generally lower than (11–28% LDL-C reduction) other investigations in the real-world setting (4,16,23,24). This may be because our database included prescription order data rather than pharmacy dispensing data. Assuming that this potential bias may have impacted the effectiveness estimates of all statins (i.e. no documented evidence of differences across statins), the relative differences in the effectiveness of one statin compared with the other would remain unchanged. Moreover, our LDL-C estimates represent usual care, reflecting what physicians may observe with their patients, including the impact of compliance with therapy, diet and exercise on overall therapy effectiveness. A recent investigation examined the effectiveness of RSV vs. ATV in usual care setting and found greater LDL-C reduction (34% vs. 27%) and goal attainment (odds ratio = 1.9) in RSV patients compared with ATV (25). This study did not examine statin effectiveness in the Medicare-eligible patients and < 65 years of age patients and did not evaluate all statins as has been done in the present study. Difference in the magnitude of effectiveness between the two studies may be related to differences in the nature of data sources (EMR vs. claims databases) and populations. Likewise, the Bullano 2006 study compared RSV effectiveness with all other statins and found RSV was more effective in reducing LDL-C and attaining LDL-C goals in a usual care setting (16). The present study confirms these findings using a prescription (as opposed to dispensing) type of dataset and in defined subpopulations of patients (defined by age categories of < 65 and ≥ 65 years) in usual care. The differences in study populations and data source between the present study and previous studies further highlight the uniqueness of the present study and, importance and relevance of the present study results in patient care decisions.

Differences between clinical trial efficacy and real-world effectiveness of statins has been previously reported (23). The purpose of the present investigation was to determine if the greater LDL-C lowering efficacy of RSV shown in clinical trials (18) held true for effectiveness in usual clinical practice as well. Our findings confirm previous reports of reduced effectiveness of statins in usual care (as opposed to efficacy observed in clinical trials) across all statins and also confirm greater LDL-C lowering effectiveness of RSV when compared with other statins in usual clinical practice.

Recent generic availability of SMV has provided further opportunities to achieve efficiency in management of patients with dyslipidaemia. To realise efficiencies without compromising quality of care, appropriate patient-specific selection for generic statins and branded statins is required. Our analysis of real-world clinical practice data indicated that high- and moderate-risk RSV patients were more likely to attain LDL-C goals when compared with other statins (including generic statins). However, no difference in goal attainment rate between RSV and SMV was observed in low-risk patients. This suggests that generic SMV may be used in low-risk patients and RSV may be used in high- and moderate-risk patients to achieve effective and efficient management of dyslipidaemia in the population. An extensive and formal cost-effectiveness evaluation of statins was beyond the scope of this study. However, using the observed effectiveness from this study and the wholesale acquisition costs for statin therapy (First DataBank National Drug Data File), a cost-effectiveness ratio (cost per LDL-C reduction) for RSV would be $3359 for patients < 65 years of age and $3683 for Medicare-eligible patients and $5251 and $6969 for ATV patients < 65 years of age and Medicare-eligible respectively. For generic SMV, a rough cost-effectiveness ratio would be between $373 and $458 for patients < 65 years of age and between $584 and $716 for Medicare-eligible patients when using $0.06–$0.10 (26) for generic SMV tablet. These cost-effectiveness data further demonstrate that RSV may be used as the branded statin for effective and efficient management of dyslipidaemia among patients requiring a large reduction in LDL-C and generic SMV may be the efficient and appropriate generic statin for patients requiring a smaller LDL-C reduction.

Our study has limitations that should be considered. The study population includes patients treated by physicians utilising an electronic medical record system in their clinical practice. Although over 3000 physicians across the US are included, there may be differences in clinical practice patterns between physicians who utilise GEMS and physicians who are not electronically equipped. However, our study population included a more heterogeneous group of patients with Medicare health insurance and those with Medigap and/or commercial insurance rather than investigations that focussed only on employed patient populations in managed care (4,19,20). Selection bias may have occurred because of the observational nature of the study. Yet, multivariate analyses were employed to control for differences in demographics and clinical characteristics. Moreover, the study pharmacy data is the physician prescription order and not pharmacy claims data. Therefore, it

was not possible to ascertain that all statin prescription orders were filled by the patient. To reduce introduction of potential bias because of non-filling of some prescriptions, only those patients with at least 90 days supply of statin therapy were included. An additional limitation is the lack of inpatient procedure data in the GEMS database. Patients with angioplasty, coronary artery bypass graft and other revascularisation procedures are classified as high-risk patients according to NCEP ATP III (2). These patients could not be distinguished in our dataset thereby reducing the size and composition of our high-risk group. Furthermore, diagnoses from specialists (e.g. cardiologists) were under-represented in our data as the majority of physicians were primary care clinicians. Cardiovascular events could not be ascertained completely in our dataset, so the impact of different statins on the incidence of cardiovascular events could not be assessed. Longer follow-up studies with availability of both inpatient and outpatient data are needed to address the potential differential impact of statins on cardiovascular events.

Conclusions

The study results indicated that RSV is more effective in lowering LDL-C and total cholesterol among elderly and non-elderly patients than other statins. RSV is also more effective in attaining LDL-C goal among high- and moderate-risk patients for both elderly and non-elderly patients than other statins. For low-risk patients, in general there were no substantial differences in LDL-C goal attainment across statins (in particular between RSV vs. ATV, SMV and FLV). Rosuvastatin effectiveness (LDL-C reduction and goal attainment) has implications for physicians in selecting the optimal statin agent to meet their individual patient needs in both the Medicare-eligible patients and patients < 65 years of age. For both Medicare-eligible patients and < 65 years of age patients, RSV may be used in moderate- and high-risk patients and generic statins may be used in low-risk patients to achieve effective and efficient management of dyslipidaemia. These findings provide physicians and healthcare plans with a better understanding of the differential effectiveness of statin therapy for patient care and formulary management.

References

1 American Heart Association. *Heart Disease and Stroke Statistics: 2006 Update*. Dallas, TX: American Heart Association, 2006.

2 Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–97.

3 Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**: 227–39.

4 Latts LM. Assessing the results: phase 1 hyperlipidemia outcomes in 27 health plans. *Am J Med* 2001; **110**: 17S–23S.

5 Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000; **160**: 459–67.

6 Rubins HB, Nelson DB, Noorbaloochi S et al. Effectiveness of lipid-lowering medications in outpatients with coronary heart disease in the Department of Veterans Affairs System. *Am J Cardiol* 2003; **92**: 1177–82.

7 Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study group. *N Engl J Med* 1998; **339**: 1349–57.

8 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383–9.

9 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002; **360**: 7–22.

10 Colhoun HM, Betteridge DJ, Durrington PN et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. *Lancet* 2004; **364**: 685–96.

11 De Lemos JA, Blazing MA, Wiviott SD et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004; **292**: 1307–16.

12 Quilliam BJ, Perez HE, Andros V, Jones P. Quantifying the effect of applying the NCEP ATP III Criteria in a managed care population treated with statin therapy. *J Manag Care Pharm* 2004; **10**: 244–50.

13 Harley CR, Williams SA, McDonough KL et al. Cholesterol management in a population of managed care enrollees. *J Clin Outcome Manag* 2003; **10**: 147–54.

14 Marcelino JJ, Feingold KR. Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. *Am J Med* 1996; **100**: 605–10.

15 Straka RJ, Taheri R, Cooper SL et al. Assessment of hypercholesterolemia control in a managed care organization. *Pharmacotherapy* 2001; **21**: 818–27.

16 Bullano MF, Wertz DA, Yang GW et al. Effect of rosuvastatin compared with other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. *Pharmacotherapy* 2006; **26**: 469–78.

17 Knopp RH. Drug treatment of lipid disorders. *N Engl J Med* 1999; **341**: 498–511.

18 Jones PH, Davidson MH, Stein EA et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol* 2003; **92**: 152–60.

19 Fellstrom B, Zannad F, Schmieder R et al. Effect of rosuvastatin on outcomes in chronic haemodialysis patients – design and rationale of the AURORA study. *Curr Control Trials Cardiovasc Med* 2005; **6**: 9

20 Ridker PM, on behalf of the JUPITER study group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated

high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003; **108**: 2292–7.
21 Schuster H, Fox J. Investigating cardiovascular risk reduction – the Rosuvastatin GALAXY Programme. *Expert Opin Pharmacother* 2004; **5**: 1187–200.
22 Cholesterol Treatment Trialists' Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267–78.
23 Frolkis JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med* 2002; **113**: 625–9.
24 Koren MJ, Hunninghake DB, ALLIANCE investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics. The ALLIANCE study. *J Am Coll Cardiol* 2004; **44**: 1772–9.
25 Bullano MF, Kamat S, Wertz DA et al. Effectiveness of rosuvastatin versus atorvastatin in reducing lipid levels and achieving low-density lipoprotein cholesterol goals in a usual care setting. *Am J Health Syst Pharm* 2007; **64**: 276–84.
26 Rubenstein S. Why generic doesn't always mean cheap. *Wall St J* 2007. http://online.WSJ.com/public/article (accessed April 14, 2007).

Paper received May 2007, accepted July 2007

