

Comparison of Lipid-Modifying Efficacy of *Rosuvastatin* Versus *Atorvastatin* in Patients With Acute Coronary Syndrome (from the LUNAR Study)

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Patients with acute coronary syndrome are recommended for early aggressive low-density lipoprotein (LDL) cholesterol-lowering therapy. The LUNAR study compared the efficacy of rosuvastatin with that of atorvastatin in decreasing LDL cholesterol in patients with acute coronary syndrome. Adult patients with coronary artery disease who were hospitalized for an acute coronary syndrome within 48 hours of first symptoms were randomized (n = 825) to an open-label, once-daily treatment with rosuvastatin 20 mg (RSV20), rosuvastatin 40 mg (RSV40), or atorvastatin 80 mg (ATV80) for 12 weeks. Patients were evaluated at weeks 2, 6, and 12. The primary end point was treatment efficacy in lowering LDL cholesterol averaged over 6 to 12 weeks. Changes in other lipoproteins, including high-density lipoprotein (HDL) cholesterol, and safety were evaluated. Analysis of covariance was used to compare least squares mean differences between each rosuvastatin treatment arm and the atorvastatin arm. The efficacy of RSV40 in lowering LDL cholesterol was significantly greater than that of ATV80 (46.8% vs 42.7% decrease, p = 0.02). LDL cholesterol lowering by RSV20 was similar to that by ATV80. Increases in HDL cholesterol were significantly greater with RSV40 (11.9%, p <0.001) and RSV20 (9.7%, p <0.01) than with ATV80 (5.6%). RSV40 was also significantly more effective than ATV80 in improving most other secondary efficacy variables, whereas the effects of RSV20 on these parameters were generally similar to those of ATV80. All 3 treatments were generally well tolerated over 12 weeks. In conclusion, results from the LUNAR study show that RSV40 more effectively decreased LDL cholesterol, increased HDL cholesterol, and improved other blood lipid parameters than ATV80 in patients with acute coronary syndrome. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;109:1239–1246)

Acute coronary syndrome is associated with an increased risk of cardiovascular mortality and recurrent cardiac events,^{1,2} underscoring the importance of identifying treatments that minimize this risk. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial suggested a benefit of lipid lowering with high-dose atorvastatin in patients with acute coronary syndrome.³ Timing of statin administration and extent of lipid lowering in relation to onset of benefit on clinical outcomes and potential mechanisms by which statins are thought to be of benefit in patients with acute

coronary syndrome are, however, controversial. A meta-analysis of statin use in patients with acute coronary syndrome confirmed the benefits of early high-dose statin administration in decreasing recurrent myocardial ischemia.⁴ In this analysis, the clinical benefit and safety of statins were suggested to be dose and statin dependent. Although there have been considerable data comparing the effectiveness of various statins, including atorvastatin 80 mg/day (ATV80) with rosuvastatin 20 mg/day (RSV20) and rosuvastatin 40 mg/day (RSV40),^{5–8} overall there has not been a systematic comparison of their lipid-lowering effects in patients with acute coronary syndrome. The Limiting Undertreatment of Lipids in Acute Coronary Syndrome with Rosuvastatin (LUNAR) study was therefore initiated to compare the efficacy of once-daily regimens of RSV20 and RSV40 with ATV80 in decreasing low-density lipoprotein (LDL) cholesterol levels in patients with acute coronary syndrome.

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Methods

The study was approved by the local institutional review board/independent ethics committee and conducted in accordance with principles of good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from patients before study-specific procedures were started.

Eligible patients were 18 to 75 years old who had coronary artery disease and were hospitalized for acute coronary

syndrome within 48 hours of the ischemic symptoms. Patients with non-ST-segment elevation acute coronary syndrome and those with ST-segment elevation acute coronary syndrome who received optimal reperfusion therapy (successful treatment with a thrombolytic agent or primary catheter-based intervention initiated within 12 hours of symptom onset) were eligible to enter the study. Patients with non-ST-segment elevation acute coronary syndrome included those with non-ST-segment elevation myocardial infarction and those with unstable angina in whom conservative management was planned. Patients were also required to have an LDL cholesterol level >70 mg/dl and a fasting triglyceride level <500 mg/dl within 72 hours of symptom onset.

Exclusion criteria included treatment for dyslipidemia with prescription medication within the preceding 4 weeks; current treatment with a depot formulation of progesterone or initiation of other hormone therapy within the previous 3 months; Q-wave myocardial infarction, pulmonary edema, moderate or severe congestive heart failure, acute moderate to severe mitral regurgitation (3 to 4+), acute ventricular septal defect, occurrence of ventricular fibrillation, sustained ventricular tachycardia, complete heart block, new-onset atrial fibrillation with an uncontrolled ventricular rate (>100 beats/min), paced ventricular rhythm, stroke, sepsis, acute pericarditis, or any evidence of systemic or pulmonary embolus within the preceding 4 weeks; coronary artery bypass graft within the preceding 3 months; percutaneous coronary intervention within the preceding 6 months to minimize the likelihood that a complication of that intervention would occur during the course of the study; planned therapeutic coronary intervention (other than primary angioplasty) or bypass surgery during current hospitalization; or failed revascularization during current hospitalization. Other exclusion criteria were a history of hypersensitivity reactions to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, women who were pregnant or breastfeeding, uncontrolled diabetes mellitus, hypertension, hypothyroidism, systolic hypotension, active liver disease or dysfunction, serum creatinine level >2 mg/dl, severe anemia (hematocrit <28%), and serum creatine kinase >3 times the upper limit of normal not caused by myocardial injury.

This trial was a prospective, multicenter, randomized, open-label, 3-arm, parallel-group, phase IIIb study (<http://clinicaltrials.gov>, identifier NCT00214630) conducted from December 14, 2003, through August 31, 2007, in 169 study centers (166 in the United States, 2 in Costa Rica, 1 in Panama). Consented patients (hospitalized for acute coronary syndrome within 48 hours of initial symptoms) entered a screening period of up to 3 days, during which core laboratory studies were obtained to document the absence of safety issues precluding statin therapy. Eligible patients were randomized in a 1:1:1 ratio to once-daily treatment with RSV20, RSV40, or ATV80 for 12 weeks. Patients were assessed at weeks 2, 6, and 12 after treatment initiation. Average time from symptom onset to first blood analyses was 1.3 days, and average time from symptom onset to randomization to study drug treatment was 3.9 days.

Investigators were blinded to measurements of primary and secondary end-point parameters. The primary end point was efficacy of RSV20 and RSV40 compared with that of ATV80 in lowering LDL cholesterol (direct measurement)

Table 1
Baseline characteristics of randomized patients (n = 825)

Variable	RSV20 (n = 277)	RSV40 (n = 270)	ATV80 (n = 278)
Gender			
Men	207 (74.7%)	200 (74.1%)	219 (78.8%)
Women	70 (25.3%)	70 (25.9%)	59 (21.2%)
Age (years)			
Mean \pm SD	53.0 \pm 9.0	52.8 \pm 8.8	52.9 \pm 9.4
Range	28–73	23–72	19–75
Race or ethnicity			
White	216 (78.0%)	226 (83.7%)	221 (79.5%)
Black	34 (12.3%)	26 (9.6%)	34 (12.2%)
Hispanic	18 (6.5%)	10 (3.7%)	14 (5.0%)
Asian	1 (0.4%)	2 (0.7%)	3 (1.1%)
Other	8 (2.9%)	6 (2.2%)	6 (2.2%)
Type of acute coronary syndrome			
ST-segment elevation myocardial infarction	113 (40.8%)	100 (37.0%)	107 (38.5%)
Non-ST-segment elevation myocardial infarction	89 (32.1%)	101 (37.4%)	104 (37.4%)
Unstable angina	75 (27.1%)	69 (25.6%)	67 (24.1%)
Body mass index (kg/m ²)	(n = 266)	(n = 264)	(n = 269)
Mean \pm SD	29.4 \pm 5.3	30.4 \pm 6.0	30.4 \pm 5.9
>30	106 (38.3%)	118 (43.7%)	111 (39.9%)
Medical history			
Myocardial infarction/acute coronary syndrome	30 (10.8%)	39 (14.4%)	29 (10.4%)
Coronary artery disease	46 (16.6%)	55 (20.4%)	37 (13.3%)
Percutaneous coronary intervention	65 (23.5%)	55 (20.4%)	50 (18.0%)
Coronary bypass	5 (1.8%)	6 (2.2%)	9 (3.2%)
Hypertension	144 (52.0%)	137 (50.7%)	139 (50.0%)
Diabetes	32 (11.6%)	35 (13.0%)	36 (16.5%)
Hyperlipidemia*	83 (30.0%)	83 (30.7%)	65 (23.4%)
Smoker	40 (14.4%)	44 (16.3%)	50 (18.0%)

* Reported by investigators as history of dyslipidemia, hyperlipidemia, or increased cholesterol.

averaged over measurements at 6 and 12 weeks. Secondary end points included (1) efficacy of RSV20 and RSV40 versus ATV80 on percent change from baseline in LDL cholesterol at 2, 6, and 12 weeks; (2) percent change from baseline in total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, non-HDL cholesterol, apolipoprotein AI, apolipoprotein B, LDL cholesterol/HDL cholesterol, total cholesterol/HDL cholesterol, non-HDL cholesterol/HDL cholesterol, apolipoprotein B/apolipoprotein AI, and LDL cholesterol (Friedewald calculation⁹) averaged over 6 to 12 weeks and at 2, 6, and 12 weeks; and (3) percent change from baseline in the inflammatory marker high-sensitivity C-reactive protein averaged over 6 to 12 weeks.

Safety and tolerability were evaluated by recording the incidence and severity of adverse events, abnormal physical examination findings, and abnormal laboratory values through 12 weeks of treatment.

The primary efficacy analysis was based on the intention-to-treat population (patients who had a baseline measurement, had ≥ 1 measurement after baseline, and had taken ≥ 1 dose of study medication). Analyses were performed using a last-observation-carried-forward method on the intention-to-treat population for all efficacy variables.

Table 2
Baseline values and percent changes (average of measurements at weeks 6 and 12) in lipids and related parameters

Variable	RSV20 (n = 246)	RSV40 (n = 251)	ATV80 (n = 257)
Low-density lipoprotein cholesterol (mg/dl)			
Mean baseline	138.4	138.8	133.2
Percent change, mean \pm SD	-42.0 \pm 18.5	-46.8* \pm 18.2	-42.7 \pm 17.7
High-density lipoprotein cholesterol (mg/dl)			
Mean baseline	39.5	38.8	39.9
Percent change, mean \pm SD	9.7 [†] \pm 16.4	11.9 [‡] \pm 19.7	5.6 \pm 19.1
Non-high-density lipoprotein cholesterol (mg/dl)			
Mean baseline	161.2	162.8	156.0
Percent change, mean \pm SD	-37.9 \pm 73.3	-42.6 \pm 17.6	-39.8 \pm 17.4
Total cholesterol (mg/dl)			
Mean baseline	200.7	201.7	195.9
Percent change, mean \pm SD	-28.6* \pm 15.4	-32.2 \pm 15.7	-30.9 \pm 15.1
Triglycerides (mg/dl)			
Subjects			254
Mean baseline	180.8	182.7	157.5
Percent change, mean \pm SD	-9.5 [†] \pm 40.4	-14.6 \pm 48.3	-18.0 \pm 38.7
Low-density lipoprotein cholesterol/high-density lipoprotein cholesterol			
Mean baseline	3.68	3.77	3.59
Percent change, mean \pm SD	-46.5 \pm 16.5	-51.5 [‡] \pm 16.6	-44.5 \pm 18.0
Non-high-density lipoprotein cholesterol/high-density lipoprotein cholesterol			
Mean baseline	4.32	4.46	4.25
Percent change, mean \pm SD	-42.3 \pm 16.8	-47.3 [‡] \pm 17.3	-41.2 \pm 19.0
Total cholesterol/high-density lipoprotein cholesterol			
Mean baseline	5.32	5.46	5.25
Percent change, mean \pm SD	-34.0 \pm 14.1	-38.2 [‡] \pm 14.5	-33.1 \pm 15.6
Apolipoprotein B (mg/dl)			
Subjects	223	224	231
Mean baseline	130.0	132.2	127.4
Percent change, mean \pm SD	-34.2 \pm 15.9	-37.9 \pm 15.0	-36.3 \pm 17.1
Apolipoprotein AI (mg/dl)			
Subjects	223	224	231
Mean baseline	134.6	134.0	135.3
Percent change, mean \pm SD	10.3 [†] \pm 25.3	10.1 [‡] \pm 14.8	4.2 \pm 16.0
Apolipoprotein B/apolipoprotein AI			
Subjects	223	224	231
Mean baseline	1.00	1.01	0.97
Percent change, mean \pm SD	-39.4 \pm 14.1	-43.0 [†] \pm 14.6	-38.3 \pm 15.4
High-sensitivity C-reactive protein			
Subjects	238	241	249
Median baseline (mg/L)	12.30	12.90	12.30
Percent change, mean \pm SD	-84.9 \pm 768.3	-83.0 \pm 53.1	-85.0 \pm 42.6

* $p < 0.05$; [†] $p < 0.01$; [‡] $p < 0.001$ versus atorvastatin 80 mg/day.

Analysis of covariance was used to compare least squares mean differences for the primary end point and percent change from baseline in LDL cholesterol averaged over measurements at 6 and 12 weeks, with a main effect for treatment and baseline LDL cholesterol as a covariate. Sequential noninferiority and superiority tests were used to compare RSV40 with ATV80 and RSV20 with ATV80. Treatment differences were considered statistically significant at a p value < 0.05 . Secondary end points were analyzed using the same approach, but only superiority tests were performed. Safety data were summarized for the safety population (patients who took ≥ 1 dose of study medication) using descriptive statistics.

To provide 90% power to detect superiority if the real treatment difference was $\geq 4\%$, it was estimated that 621

patients (207 in each treatment arm) would be required in the intention-to-treat population.

Results

In total 1,391 patients entered the screening period, and 566 failed screening. The most common reason for screen failure (81%) was not meeting the entry criteria. In total 825 patients were randomized to treatment, and 799 of these received ≥ 1 dose of study medication and were evaluated for safety. The intention-to-treat population comprised 754 patients.

Demographic and clinical characteristics of the 825 randomized patients were well balanced among the 3 treatment arms (Table 1). Overall, most patients were men (76%), white (80%), and < 65 years old (89%). Obesity (body mass

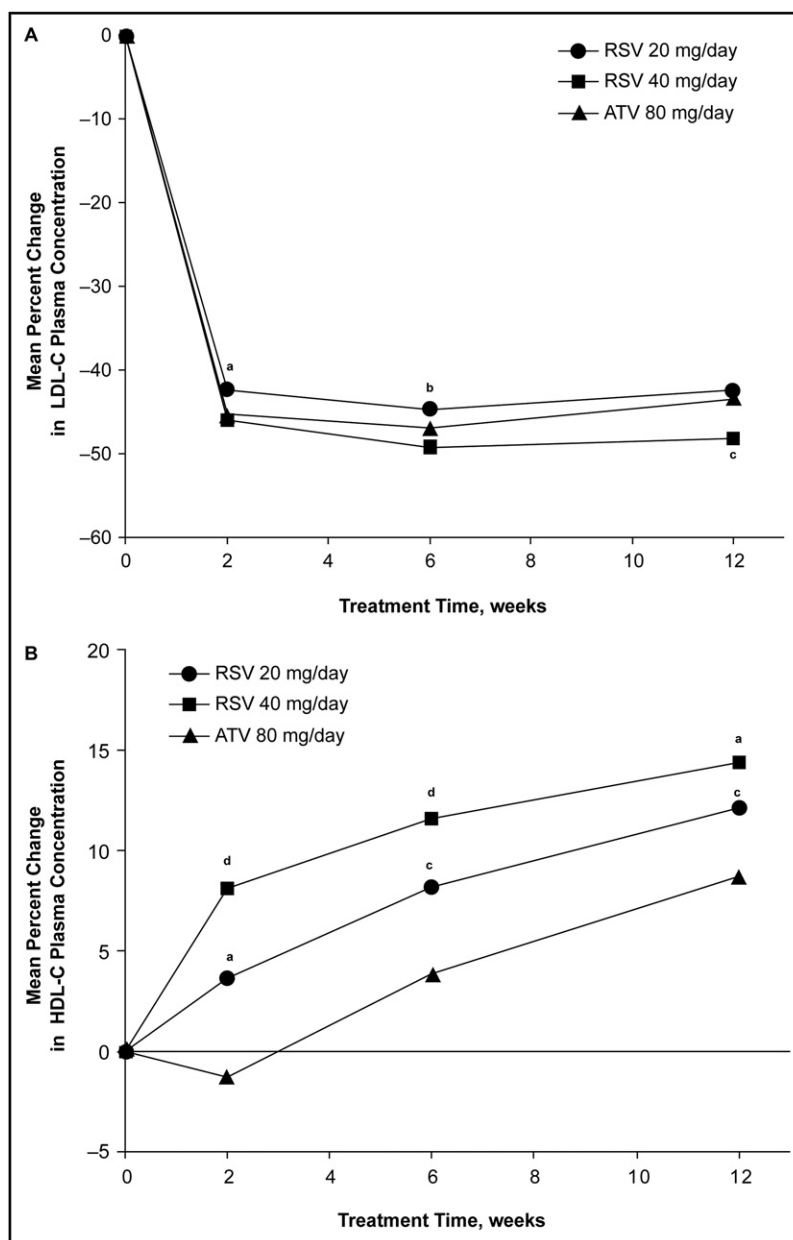


Figure 1. Mean percent change from baseline by weeks 2, 6, and 12 in (A) low-density lipoprotein cholesterol (LDL-C) and (B) high-density lipoprotein cholesterol (HDL-C). ^a $p < 0.01$ versus atorvastatin 80 mg/day; ^b $p < 0.05$ rosuvastatin 20 mg/day versus atorvastatin 80 mg/day; ^c $p < 0.05$ versus atorvastatin 80 mg/day; ^d $p < 0.001$ versus atorvastatin 80 mg/day. Calculations used least squares mean differences from an analysis of covariance model with a main effect for treatment and baseline low-density lipoprotein cholesterol or high-density lipoprotein cholesterol level as a covariate.

index >30 kg/m²) was common (335 of 825, 41%). Myocardial infarction was the most common reason for hospital admission, with similar percentages of patients having ST-segment elevation myocardial infarction (320 of 825, 39%) and non-ST-segment elevation myocardial infarction (294 of 825, 36%); unstable angina was a less common reason for admission (211 of 825, 26%). As entry criteria, all patients with ST-segment elevation myocardial infarction were required to have had successful treatment with a thrombolytic agent or primary catheter-based intervention within 12 hours of symptom onset.

At baseline mean LDL cholesterol was similar in the 3 treatment arms and within the range of 133 to 139 mg/dl

(Table 2). Mean change from baseline in LDL cholesterol averaged over weeks 6 and 12 was significantly greater with RSV40 compared with ATV80 ($p = 0.02$; Table 2). LDL cholesterol lowering by RSV20 was similar to that by ATV80. Similar results were achieved in all subcategories of acute coronary syndrome (unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction). There was also no difference observed in obese versus nonobese patients. Sensitivity analysis of LDL cholesterol calculated using the Friedewald equation⁹ yielded results that concurred with those from the primary analysis of LDL cholesterol by direct measurement (Supplemental Table 1).

Table 3

Serious adverse events, serious cardiovascular adverse events, study withdrawals owing to adverse events, and deaths

Variable	RSV20 (n = 267)	RSV40 (n = 263)	ATV80 (n = 269)
Any serious adverse event	28 (10.5%)	23 (8.7%)	38 (14.1%)
Serious cardiovascular adverse event	9 (3.4%)	5 (1.9%)	6 (2.2%)
Unstable angina	4 (1.5%)	3 (1.1%)	3 (1.1%)
Myocardial infarction	5 (1.9%)	2 (0.8%)	2 (0.7%)
Cerebrovascular accident	0	0	1 (0.4%)
Withdrawal owing to adverse event	10 (3.7%)	16 (6.1%)	25 (9.3%)
Musculoskeletal and connective tissue disorders	5 (1.9%)	6 (2.3%)	17 (6.3%)
Death	0	2 (0.8%)	1 (0.4%)

LDL cholesterol had decreased to approximately its final values in all 3 groups by 2 weeks after starting treatment; subsequent changes from week 2 to weeks 6 and 12 were of smaller magnitude (Figure 1). Decrease in LDL cholesterol with RSV40 was significantly greater than that with ATV80 at week 12 ($p = 0.02$) but not at weeks 2 and 6. Decrease in LDL cholesterol with RSV20 was similar to that with ATV80 at week 12 but was significantly less at weeks 2 ($p < 0.01$) and 6 ($p = 0.04$).

Mean baseline HDL cholesterol was similar across the 3 treatment arms (~ 39 mg/dl; Table 2). Mean change from baseline in HDL cholesterol averaged over weeks 6 and 12 showed that HDL cholesterol increased by a significantly greater extent with RSV20 ($p < 0.01$) and RSV40 ($p < 0.001$) than with ATV80 (Table 2).

At week 2, HDL cholesterol increased by 3.6% with RSV20 and 8.1% with RSV40 but decreased by 1.3% with ATV80 (Figure 1). At weeks 6 and 12, HDL cholesterol increased with all 3 treatments. Compared with ATV80, increases in HDL cholesterol were significantly greater with RSV20 ($p < 0.05$) and RSV40 ($p < 0.01$) at weeks 2, 6, and 12.

RSV40 was significantly more effective than ATV80 in improving apolipoprotein AI ($p < 0.001$) and several lipid ratios, including LDL cholesterol/HDL cholesterol ($p < 0.001$), non-HDL cholesterol/HDL cholesterol ($p < 0.001$), total cholesterol/HDL cholesterol ($p < 0.001$), and apolipoprotein B/apolipoprotein AI ($p < 0.01$; Table 2). RSV20 was significantly more effective than ATV80 in increasing apolipoprotein AI ($p < 0.01$) but was significantly less effective in decreasing total cholesterol ($p < 0.05$) and triglycerides ($p < 0.01$; Table 2). Changes in non-HDL cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein with RSV20 and RSV40 were not significantly different from those with ATV80 (Table 2).

Serious adverse events occurred in 14.1% of patients treated with ATV80, 10.5% of those treated with RSV20, and 8.7% of those treated with RSV40 (Table 3). Serious cardiovascular adverse events were infrequently observed in any treatment group (Table 3). None of the serious adverse events or serious cardiovascular adverse events was considered by the investigators to be related to study treatment. Discontinuation of study treatment because of an adverse event occurred in 3.7%, 6.1%, and 9.3% of patients treated

Table 4

Adverse events that occurred in more than 5% of patients in any treatment group

Variable	RSV20 (n = 267)	RSV40 (n = 263)	ATV80 (n = 269)
Myalgia	27 (10.1%)	24 (9.1%)	27 (10.0%)
Angina pectoris	27 (10.1%)	23 (8.7%)	18 (6.7%)
Noncardiac chest pain	13 (4.9%)	22 (8.4%)	18 (6.7%)
Fatigue	19 (7.1%)	9 (3.4%)	12 (4.5%)
Dizziness	6 (2.2%)	13 (4.9%)	15 (5.6%)
Headache	7 (2.6%)	9 (3.4%)	16 (5.9%)
Hypertension	15 (5.6%)	9 (3.4%)	6 (2.2%)

Table 5

Increases in alanine aminotransferase, creatine kinase, and serum creatinine

Variable	RSV20 (n = 249)	RSV40 (n = 249)	ATV80 (n = 257)
Alanine aminotransferase > 3 times upper limit of normal at 2 consecutive visits	1 (0.4%)	0	1 (0.4%)
Creatine kinase > 10 times upper limit of normal	0	1 (0.4%)	0
Subjects	234	229	244
Serum creatinine increased $> 30\%$ from baseline and above upper limit of normal at maximum	2 (0.9%)	0	3 (1.2%)

with RSV20, RSV40, and ATV80, respectively (Table 3). Musculoskeletal and connective tissue abnormalities accounted for most study discontinuations because of an adverse event. Three patients died during the study (Table 3): a 66-year-old man treated with RSV40 died of myocardial infarction on treatment day 1, a 51-year-old man treated with RSV40 died of cardiac arrest secondary to ventricular fibrillation on treatment day 3, and a 41-year-old man treated with ATV80 died of torsade de pointes on treatment day 2. None of these deaths was judged by the investigators to be related to study treatment.

Overall frequency of adverse events was similar among treatment arms: 65.5% with RSV20, 63.9% with RSV40, and 65.4% with ATV80. A minority of patients reported an adverse event that was considered by the investigators to be related to study treatment: 9.4% with RSV20, 14.8% with RSV40, and 15.6% with ATV80. Myalgia, angina pectoris, noncardiac chest pain, and fatigue were the most frequently reported adverse events that occurred in $> 5\%$ of patients in any treatment arm regardless of relation to study medication (Table 4).

Overall, the number of clinically notable laboratory abnormalities was low and showed no treatment-related trends (Table 5). Two patients, 1 treated with RSV20 and 1 treated with ATV80, had clinically important increases in alanine aminotransferase (> 3 times upper limit of normal on 2 consecutive visits). These increases were reported as adverse events and ultimately led to withdrawal of these patients from the study. One patient treated with RSV40 had a clinically important increase of creatine kinase (> 10 times upper limit of normal) at week 12 but with no associated

Table 6

Serum creatinine and estimated glomerular filtration rate at baseline and change at final visit

	RSV20	RSV40	ATV80
Serum creatinine ($\mu\text{mol/L}$)			
Subjects	266	263	269
Baseline, mean \pm SD	88.5 \pm 16.2	87.0 \pm 16.0	90.1 \pm 17.4
Subjects	220	202	210
Change at final visit, mean \pm SD	6.3 \pm 12.0	4.9 \pm 11.2	5.8 \pm 14.3
Estimated glomerular filtration rate (ml/min/1.73 m ²)			
Subjects	266	263	269
Baseline, mean \pm SD	81.9 \pm 15.7	83.5 \pm 17.0	81.7 \pm 17.1
Subjects	220	202	210
Change at final visit, mean \pm SD	-6.6 \pm 12.6	-5.3 \pm 11.5	-6.5 \pm 13.4

skeletal muscle adverse events. Baseline serum creatinine concentrations and estimated glomerular filtration rates were similar in patients in the 3 treatment arms; only small changes from baseline in either value were noted (Table 6). No patients had clinically important increases of serum creatinine (increase >100% from baseline).

Discussion

Increasing evidence suggests that, overall, high-dose statin therapy, such as with ATV80, used to achieve an LDL cholesterol level <70 mg/dl is more effective than standard therapy with, for example, simvastatin 20 to 40 mg.¹⁰⁻¹³ The role of statins in patients with acute coronary syndrome, however, remains controversial in several aspects. A meta-analysis of the use of statins in patients with acute coronary syndrome confirmed the benefit of early high-dose statin use in decreasing recurrent ischemia and possibly coronary revascularization but did not find a significant benefit on hard clinical outcomes, including myocardial infarction and stroke.⁴ A mortality benefit in patients with acute coronary syndrome was observed over the long term (24 months) but not over the short term (4 months). The results of this meta-analysis raise several important questions, including the optimal LDL cholesterol threshold for initiating statin therapy, timing of statin administration, and target LDL cholesterol level and its relation to the onset of clinical outcomes and, therefore, the choice and dose of statin for the treatment of patients with acute coronary syndrome.

The results of the present comparison of RSV20 and RSV40 with ATV80 in patients with acute coronary syndrome therefore may be of interest for several reasons. The finding that RSV20 was as effective as ATV80 in decreasing LDL cholesterol with a similar safety profile suggests that this dose of rosuvastatin might be considered an alternative to ATV80 in patients with acute coronary syndrome. The finding that RSV40 was significantly more effective than ATV80 in decreasing LDL cholesterol and several other important lipid parameters, such as apolipoprotein AI, LDL cholesterol/HDL cholesterol, non-HDL cholesterol/HDL cholesterol, total cholesterol/HDL cholesterol, and apolipoprotein B/apolipoprotein AI, is consistent with pre-

vious data from patients without acute coronary syndrome⁵ and with the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) study, which examined patients with stable coronary disease.¹⁴ In that intravascular ultrasound study, 2 years of therapy with RSV40 produced a greater regression of total coronary atheroma volume than ATV80 ($p = 0.01$); regarding the percent atheroma volume, there was an overall trend toward greater regression ($p = 0.17$), with greater regression with rosuvastatin in those patients with higher baseline LDL cholesterol levels ($p = 0.02$). Overall, 72.1% of RSV40-treated patients achieved LDL cholesterol levels <70 mg/dl versus 56.1% of ATV80-treated patients ($p < 0.001$), with a low incidence of adverse events.

These results suggest that this dose of rosuvastatin may be preferable in high-risk patients with acute coronary syndrome in whom a target LDL cholesterol level <70 mg/dl is thought desirable but has not yet been achieved by previous statin therapy and in those with an initially increased LDL cholesterol in whom it would be unlikely, based on the baseline LDL cholesterol level, that the target LDL cholesterol of <70 mg/dl would be achieved by a high-dose statin such as ATV80. It should be emphasized, however, that a target LDL cholesterol level <70 mg/dl in patients with acute coronary syndrome remains controversial¹⁵ and that in a large percentage of patients, a more moderate dose of a statin may be sufficient to decrease risk. Failure of the current use of statins, including ATV80, to lower the incidence of myocardial infarction, stroke, or short-term mortality (4 months) in patients with acute coronary syndrome¹⁵ suggests the need for further exploration of the effectiveness of more potent LDL cholesterol-decreasing drugs. Although a definitive conclusion on the comparative effectiveness of 2 agents such as RSV40 and ATV80 cannot be made without results from an adequately powered large-scale randomized trial on clinical outcomes, the results of the present study evaluating several important lipid parameters, including LDL cholesterol and apolipoprotein B/apolipoprotein AI, provide a basis on which one might postulate an advantage of RSV40 compared with ATV80 and therefore undertake a larger-scale, longer-term clinical outcomes study.

The significantly greater increase in HDL cholesterol with RSV40 compared with ATV80, beginning 2 weeks after randomization and persisting over the 12-week study period, also suggests an additional potential benefit of RSV40. There is increasing evidence that an increase in HDL cholesterol may have important effects on oxidative stress, endothelial function, myocardial ischemia, plaque stability, and progression of atherosclerosis.^{16,17} The importance of this degree of increasing HDL cholesterol in terms of clinical outcome benefits must also await larger-scale, longer-term studies.

With regard to the safety of statins in patients with acute coronary syndrome, the review by Morrissey et al¹⁵ emphasized an increased incidence of myopathy with high doses of simvastatin in the Aggrastat to Zocor (A to Z)¹⁸ and Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)¹⁹ trials. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial,²⁰ a high dose of atorvastatin (80 mg) was associated with a greater incidence of liver toxicity than

pravastatin 40 mg. In the MIRACL study,³ the use of ATV80 was also associated with an increased incidence of liver enzyme abnormalities. Overall, however, ATV80 appears to be relatively well tolerated, with a 1.43% increase in liver enzyme abnormalities and 4 of 18,696 cases with a creatinine kinase increase >10 times the upper limit of normal.²¹ Similarly, previous experience with RSV20 and RSV40 has suggested that these doses are associated with a relatively low incidence of serious adverse events.²² In the present relatively small study, there was a trend toward a lower incidence of withdrawals owing to musculoskeletal and connective tissue disorders with the 2 doses of rosuvastatin, which should be interpreted in the context of the study's open-label design.

The limitation of the study owing to an open-label design should not bias its objective findings. Although the trial was open label, it was a prospective, randomized, observational study with blinded end points. The open-label design did permit bias in the investigators' interpretation and response to adverse events that might occur, but the similarity in adverse events in the treatment arms suggests that this did not occur to any significant degree. The blinded end points assured the validity of the findings on the lipid and lipoprotein effects of the 3 therapies. The study was also limited in that the number of patients was too small and the duration of follow-up was too short to reach any conclusions on the comparative safety of RSV20 and RSV40 versus ATV80 and much too small and short to permit an exploration of clinical outcomes benefits. Uncertainty about the level of LDL cholesterol necessary to decrease clinical outcomes in patients with acute coronary syndrome, as pointed out by Morrissey et al,¹⁵ and the potential increased risk associated with high-dose statin use in patients with acute coronary syndrome emphasize the need for further large-scale, long-term trials in patients with acute coronary syndrome to explore further the risk–benefit ratio of high- versus standard-dose statin therapy in relation to the level of achieved lipid decrease and clinical outcomes.

Another limitation of the study is its applicability to the broad range of patients with acute coronary syndrome, given the large portion of patients who did not meet the entry criteria. Because the exclusion criteria focused on secondary causes of hypercholesterolemia, safety issues with use of statins, and the presence of significant medical conditions that might prevent a patient from safely taking statin therapy for the 12-week duration of the trial, the findings of the study are most applicable to more stable subjects with acute coronary syndrome who are candidates for high-dose statin therapy.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2011.12.015.

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