Comparison of Effects of *Atorvastatin* (20 mg) Versus *Rosuvastatin* (10 mg) Therapy on Mild Coronary Atherosclerotic Plaques (from the ARTMAP Trial)

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High-dose rosuvastatin induces regression of coronary atherosclerosis, but it remains uncertain whether usual-dose statin has similar effects. We compared the effects of atorvastatin 20 mg/day versus rosuvastatin 10 mg/day on mild coronary atherosclerotic plaques (20% to 50% luminal narrowing and lesion length >10 mm) using intravascular ultrasound (IVUS). Three hundred fifty statin-naive patients with mild coronary atherosclerotic plaques were randomized to receive atorvastatin 20 mg/day or rosuvastatin 10 mg/day. IVUS examinations were performed at baseline and 6-month follow-up. Primary end point was percent change in total atheroma volume (TAV) defined as (TAV at 6 months − TAV at baseline)/(TAV at baseline) × 100. Evaluable IVUS was obtained for 271 patients (atorvastatin in 143, rosuvastatin in 128). Clinical characteristics, lipid levels, and IVUS measurements at baseline were similar between the 2 groups. At 6-month follow-up, percent change in TAV was significantly less in the atorvastatin group than in the rosuvastatin group (−3.9 ± 11.9% vs −7.4 ± 10.6%, respectively, p = 0.018). In contrast, change in percent atheroma volume was not different between the 2 groups (−0.3 ± 4.2 vs −1.1 ± 3.5, respectively, p = 0.157). Compared to baseline, TAV and TAV at the most diseased 10-mm subsegment were significantly decreased in the 2 groups (p <0.001). Changes in lipid profiles at 6-month follow-up were similar between the 2 groups. In conclusion, usual doses of atorvastatin and rosuvastatin induced significant regression of coronary atherosclerosis in statin-naive patients, with a greater decrease in favor of rosuvastatin. **(Am J Cardiol 2012;109: 1700–1704)**

Atorvastatin (10 to 20 mg/day) and rosuvastatin (10 mg/day) are commonly prescribed to prevent recurrent coronary events.[1] However, little is known about whether this approach is as effective as high-dose statin therapy and whether plaque regression differences exist according to type of statin used. In the present study, we compared the effects of atorvastatin versus rosuvastatin therapy with equivalent potency on mild coronary atherosclerotic plaques using intravascular ultrasound (IVUS; atorvastatin versus rosuvastatin therapy with equivalent potency on mild coronary atherosclerotic plaques [ARTMAP] trial).

Methods

ARTMAP is a prospective, single-center, open-label, randomized comparison trial involving statin-naive patients ≥18 years old with clinically indicated percutaneous coronary intervention from September 2004 through June 2009. Patients were included if they had ≥1 atherosclerotic plaque with 20% to 50% luminal narrowing and lesion length >10 mm in a coronary artery by visual assessment that had not been subjected to intervention. Exclusion criteria included coronary artery bypass graft surgery, valvular heart disease, left ventricular ejection fraction <40%, any heart failure, renal insufficiency (serum creatinine >1.5 mg/dl), active liver disease, and any statin therapy in the previous 4 weeks. The study protocol was approved by our institutional review committee. All patients provided written informed consent.

Patients were randomized to receive atorvastatin 20 mg/day or rosuvastatin 10 mg/day after IVUS examination. The randomization code was generated by computer, and the study drug was administered after the procedure. Biochemical laboratory tests were performed at the time of admission and at 1- and 6-month follow-up periods. All patients were clinically monitored by laboratory measurements at 1 month and 3 and 6 months. Routine coronary angiography and IVUS examination at 6 months were requested for all patients.

The longest and least angulated target vessel meeting the inclusion criteria was selected. The region of interest was flanked by 2 anatomic landmarks (side branches) that were easily identifiable at follow-up. After intracoronary administration of nitroglycerin 0.2 mg, IVUS imaging was performed using a motorized transducer pullback system (0.5

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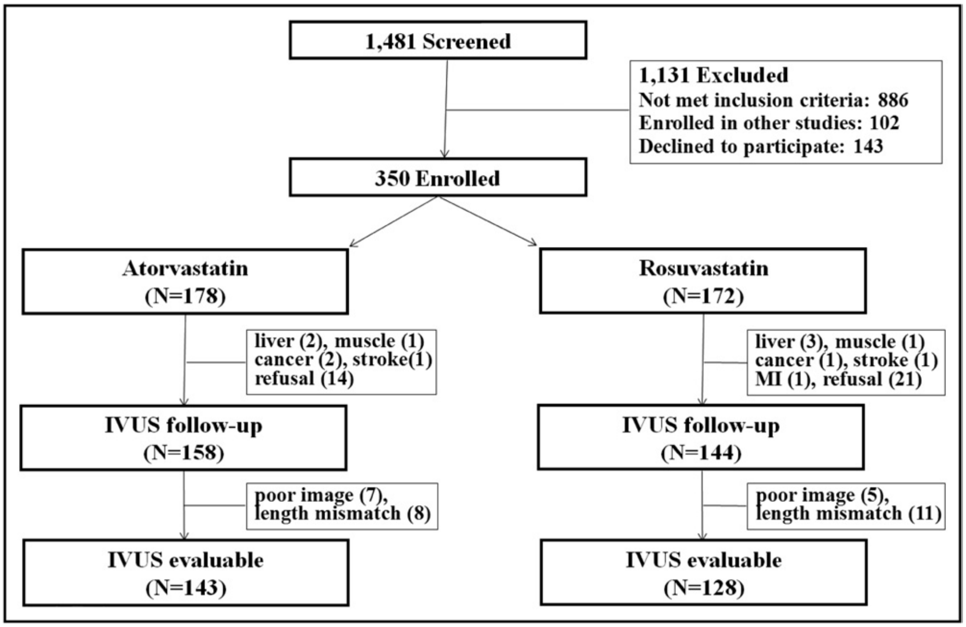

Figure 1. Study flow chart of patient enrollment.

mm/s) and a commercial scanner (SCIMED/Boston Scientific, Natick, Massachusetts) that consisted of a rotating 40-MHz transducer within a 3.2Fr imaging sheath. IVUS images were recorded on a computer disk and analyzed by personnel unaware of the study drug. After the 6-month treatment period, actively participating patients underwent repeat coronary angiography and IVUS examination.

Core laboratory personnel (CVRF, Seoul, Korea) blinded to treatment assignment analyzed all IVUS images using validated software (EchoPlaque 3.0, Indec Systems, Mountain View, California). A technician selected a distal branch site as the beginning point for analysis, and manual planimetry was used to trace the leading edges of the luminal and external elastic membrane (EEM) borders every 1 mm in the region of interest. Total atheroma volume (TAV) was calculated as the sum of differences between EEM and lumen cross-sectional areas (CSAs) across all evaluable slices. Normalized TAV was calculated as the product of the mean atheroma area and median segment length in the entire population. Percent atheroma volume (PAV) was calculated as $PAV = (\Sigma[EEM_{CSA} - lumen_{CSA}]/\Sigma EEM_{CSA}) \times 100$. To observe the variability of the IVUS measurements, intra- and interobserver coefficients of variation were calculated in 20 randomly selected lesions. Inter- and intraobserver coefficients of variation were 0.07 and 0.06 mm^3 for total lumen volume and 0.04 and 0.03 mm^3 for total vessel volume, respectively.

The primary end point was percent change in TAV defined as (TAV at 6 months minus TAV at baseline)/(TAV at baseline) × 100. Secondary end points included change in TAV (TAV at 6 months minus TAV at baseline), change in PAV (PAV at 6 months minus PAV at baseline), and change in TAV within the most diseased baseline 10-mm subsegment and percent change from baseline in lipid levels.

A sample size of approximately 140 patients per treatment group was calculated to provide 80% power (assuming an SD of 19%) to detect a difference of 6.4% with a significance level of 0.05 using a 2-sided test.[2] With an anticipated dropout rate of 20%, a final sample size of 175 patients per treatment group (total 350 patients) was specified to provide an adequate number of evaluable patients. Continuous variables are expressed as mean ± SD or median with interquartile range, whereas categorical variables are expressed as frequency. Continuous variables were compared using paired *t* test or Wilcoxon rank-sum test for changes in each group and unpaired *t* test or Mann–Whitney *U* test for differences between the 2 groups. IVUS end points were analyzed using an analysis of covariance model

Table 1
Baseline clinical characteristics

Characteristics	Atorvastatin (n = 143)	Rosuvastatin (n = 128)	p Value
Age (years)	57.6 ± 7.6	55.3 ± 9.4	0.024
Men/women	117/26	106/22	0.874
Current smoker	71 (49.7%)	56 (43.8%)	0.345
Diabetes mellitus	26 (18.2%)	26 (20.3%)	0.770
Hypertension	70 (49.0%)	64 (50%)	0.903
Acute myocardial infarction	47 (32.9%)	45 (35.2%)	0.893
Unstable angina pectoris	52 (36.4%)	41 (32.0%)	0.622
Stable angina pectoris	44 (30.8%)	42 (32.8%)	0.794
Target coronary artery			0.574
Left anterior descending	57 (39.9%)	44 (34.3%)	
Left circumflex	38 (26.6%)	34 (26.6%)	
Right	48 (33.6%)	50 (39.1%)	
Medications at time of follow-up			
Aspirin	143 (100%)	128 (100%)	1.000
Clopidogrel	124 (86.7%)	116 (90.6%)	0.680
Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker	48 (33.6%)	38 (30.0%)	0.434
β Blockers	71 (49.7%)	67 (52.3%)	0.807
Calcium channel antagonists	108 (75.5%)	102 (79.7%)	0.653

Table 2
Laboratory findings

Characteristics	Atorvastatin (n = 143)	Rosuvastatin (n = 128)	p Value Between Groups
Total cholesterol (mg/dl)			
Baseline	183 ± 36	186 ± 34	0.495
6 months	128 ± 23	126 ± 25	0.510
Change from baseline (%)	−29 ± 14	−31 ± 13	0.095
Low-density lipoprotein cholesterol (mg/dl)			
Baseline	110 ± 31	109 ± 31	0.755
6 months	56 ± 18	53 ± 18	0.232
Change from baseline (%)	−47 ± 18	−49 ± 17	0.256
High-density lipoprotein cholesterol (mg/dl)			
Baseline	40 ± 13	40 ± 9	0.994
6 months	47 ± 12	47 ± 11	0.795
Change from baseline (%)	19 ± 25	20 ± 25	0.752
Triglyceride cholesterol (mg/dl)			
Baseline	165 ± 93	182 ± 121	0.196
6 months	122 ± 67	125 ± 65	0.702
Change from baseline (%)	−16 ± 38	−19 ± 44	0.554
High-sensitivity C-reactive protein at 6 months (mg/L)	1.6 ± 3.2	1.2 ± 1.9	0.263

with baseline IVUS values as a covariate and treatment group as a fixed factor. Statistical significance was defined as a 2-sided p value <0.05.

Results

As shown in Figure 1, 350 patients were randomized to receive atorvastatin 20 mg/day (n = 178) or rosuvastatin 10 mg/day (n = 172) during the study period. IVUS follow-up was performed in 302 patients (86.3%). Of these, 271 patients (atorvastatin in 143, rosuvastatin in 128) had an evaluable baseline IVUS and a follow-up IVUS and comprised the study population.

Baseline clinical characteristics were not different between the 2 groups, except age (Table 1). Lipid levels were also similar between the 2 groups (Table 2). At 6-month follow-up, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were significantly decreased in the 2 groups (p <0.001), whereas high-density lipoprotein cholesterol levels were significantly increased (p <0.001). High-sensitivity C-reactive protein levels at 6 months were comparable between the 2 groups (p = 0.263).

IVUS data are presented in Table 3. IVUS-measured lengths were 32.6 ± 7.1 mm in the atorvastatin group and 34.3 ± 7.3 mm in the rosuvastatin group (p = 0.055). Baseline IVUS measurements were not different between the 2 groups. At 6-month follow-up, TAV, normalized TAV, and TAV at the most diseased 10-mm subsegment were significantly decreased in the 2 groups (p <0.001). In contrast, PAV was significantly decreased in the rosuvastatin group (p = 0.001) but not in the atorvastatin group (p = 0.359).

Percent change in TAV (primary end point) was significantly smaller in the atorvastatin group than in the rosuvastatin group (−3.9 ± 11.9% vs −7.4 ± 10.6%, respectively, p = 0.018). Plaque regression (percent change in TAV <0%) was less frequently observed in the atorvastatin group compared to the rosuvastatin group (65.0% vs 78.1%, respectively, p = 0.012). However, change in PAV was not different between the 2 groups (−0.3 ± 4.2 vs −1.1 ± 3.5, respectively, p = 0.157). Similar differences between groups were observed for change in TAV and percent change in TAV within the most diseased baseline 10-mm subsegment (Table 3).

Discussion

In the present study, TAV at 6-month follow-up was significantly decreased in atorvastatin- and rosuvastatin-treated patients, and a greater decrease was observed in the rosuvastatin group compared to the atorvastatin group. These findings suggest that usual doses of atorvastatin and rosuvastatin rapidly induce regression of coronary atherosclerosis in a large proportion of statin-naive patients.

In the The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial,[2] coronary atherosclerosis progression occurred in the usual-dose pravastatin group compared to baseline (2.7%), but not in the high-dose atorvastatin group (−0.4%) over an 18-month period. Low-density lipoprotein cholesterol level was decreased to 110 mg/dl in the pravastatin group and 79 mg/dl in the atorvastatin group. These findings indicate that intensive statin therapy with substantial decrease of low-density lipoprotein cholesterol slows the progression of coronary atherosclerosis. However, in A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) trial,[3] 63.6% of patients showed regression and mean TAV decreased by 7%, with a 1% decrease in PAV after 24 months of treatment. A marked decrease of low-density lipoprotein cholesterol (53%), with low average low-density lipoprotein cholesterol levels (60.8 mg/dl), was recorded. The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) trial was recently published, and the major results were comparable to our findings.[4] The PAV results demonstrated a numerically larger decrease in favor of rosuvastatin versus atorvastatin but did not reach statistical significance, whereas TAV displayed a statistically significant decrease in the group treated with rosuvastatin compared to atorvastatin.

Atorvastatin and rosuvastatin are potent synthetic statins with different pharmacologic properties.[5] Atorvastatin is lipophilic and metabolized by the Cytochrome P450 3A4 (CYP3A4) pathway, whereas rosuvastatin is hydrophilic and metabolized by the non-CYP3A4 pathway. High-dose statins are not commonly used because of safety concerns.[1] In the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS) trial, rosuvastatin 16.9 mg/day for 76 weeks induced significant regression of coronary plaque volume in patients with stable coronary artery disease,[6] suggesting that usual-dose statin also promotes plaque decrease. Our trial was designed to compare the efficacy of 2 potent statins administered at equivalent standard doses (atorvastatin 20 mg vs rosuvastatin 10 mg)[7] in the treatment of mild coronary artery disease over a 6-month follow-up

Table 3
Intravascular ultrasound parameters

Characteristics	Atorvastatin (n = 143)	Rosuvastatin (n = 128)	p Value Between Groups
Total atheroma volume (mm^3)			
Baseline	215 ± 89	229 ± 94	0.226
Follow-up	205 ± 85	210 ± 86	0.655
Nominal change (interquartile range)	−6.7 (−27.0 to 4.6)	−15.6 (−34.2 to −0.9)	0.012*
p value compared to baseline	<0.001	<0.001	
Percent change (primary end point)	−3.9 ± 11.9	−7.4 ± 10.6	0.018†
Normalized total atheroma volume (mm^3)			
Baseline	220 ± 80	220 ± 69	0.994
Follow-up	211 ± 78	201 ± 63	0.280
Nominal change (95% confidence interval)	−9.6 (−14.4 to −4.8)	−18.2 (−22.6 to −13.7)	0.021†
p value compared to baseline	<0.001	<0.001	
Percent change	−3.9 ± 11.9	−7.5 ± 10.7	0.017†
Percent atheroma volume (%)			
Baseline	42.3 ± 8.6	43.3 ± 9.6	0.991
Follow-up	43.0 ± 8.7	42.3 ± 9.7	0.523
Nominal change (95% confidence interval)	−0.3 (−1.0 to 0.4)	−1.0 (−1.7 to −0.4)	0.157†
p value compared to baseline	0.359	0.001	
Percent change	−0.2 ± 10.7	−2.2 ± 8.7	0.117†
Atheroma volume in 10-mm subsegment with greatest disease severity (mm^3)			
Baseline	74.9 ± 26.8	76.1 ± 25.2	0.706
Follow-up	70.7 ± 26.9	68.0 ± 23.6	0.378
Nominal change (95% confidence interval)	−4.2 (−6.1 to −2.2)	−8.1 (−10.2 to −5.9)	0.014†
p value compared to baseline	<0.001	<0.001	
Percent change (interquartile range)	−4.8 (−13.6 to 3.8)	−9.5 (−9.5 to −0.7)	0.011*

Nominal change is calculated as follow-up minus baseline, and percent change as (follow-up minus baseline)/baseline × 100.
* Mann–Whitney *U* test.
† Analysis of covariance.

period. We observed a marked decrease of low-density lipoprotein cholesterol level (average 55 mg/dl) and an increase of high-density lipoprotein cholesterol level (average 47 mg/dl) in the 2 treatment groups. TAV at 6-month follow-up was significantly decreased in the 2 groups (~70% of patients). Percent change in TAV (primary end point) was slightly greater in magnitude than those in previous statin trials and significantly greater in the rosuvastatin group compared to the atorvastatin group. These differences may reflect variations in study design including study population, statin dose, and follow-up duration. In our study, change in PAV (secondary end point) was not statistically different between the 2 groups, but PAV has some pitfalls. If EEM increases because of positive remodeling, PAV can decrease despite plaque progression. Furthermore, the best surrogate corresponding to clinical outcomes remains to be established. Our findings may be helpful to further confirm the dramatic benefits of rosuvastatin therapy, as shown in the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).[8]

It remains uncertain how rapidly atherosclerotic plaque regression occurs. In the Early Statin Treatment in Patients With Acute Coronary Syndrome (ESTABLISH) trial,[9] statin treatment induced significant regression of atherosclerotic lesions 6 months later. Intravenous recombinant apolipoprotein A1 Milano administered in 5 weekly infusions led to a 4.1% decrease in TAV.[10] In a recent report, usual-dose rosuvastatin (10 mg/day) resulted in a significant decrease of carotid intima–media thickness at 1-year follow-up, but little change was observed from 1- to 2-year follow-up.[11] These findings suggest that atherosclerotic plaque may regress rapidly within 1 year and remain unchanged at subsequent follow-up. Fibrous tissue and calcification appear irreversible despite statin therapy. In contrast, statins have been shown to decrease smooth muscle cell accumulation and lipid content,[12] indicating that smaller lipid-rich mild plaques are prone to regression compared to advanced atherosclerotic plaques. In our study, greater low-density lipoprotein lowering and concomitant high-density lipoprotein increase may be related to plaque regression. However, lipid profiles or high-sensitivity C-reactive protein at 6-month follow-up were similar between the 2 groups. Thus, our results cannot be fully explained by simple changes in lipid profiles, suggesting that other factors beyond serum lipids are responsible for statin differences. Previously, we reported the presence of functionally active 3-hydroxy-3-methylglutaryl–coenzyme A reductase in coronary atherosclerotic plaques.[13] It has been shown that rosuvastatin forms the largest number of bonds with 3-hydroxy-3-methylglutaryl–coenzyme A reductase, leading to superior efficacy.[14,15] Statins may penetrate atherosclerotic lesions and suppress active plaque inflammation by tight-binding inhibition of lesion 3-hydroxy-3-methylglutaryl–coenzyme A reductase. Macrophages express a specific profile of organic anionic transporters involved in the uptake and export of exogenous molecules.[16] Organic anionic transporter polypeptides mediate the cellular uptake of statins, and their affinity may partly explain the efficacy and safety of statins.[17] It is therefore tempting to speculate that rosuvastatin has a more significant effect on lesion 3-hydroxy-3-methylglutaryl–coenzyme A reductase compared to atorvastatin, leading to regression of coronary atherosclerotic plaques. However, this hypothesis requires further confirmation.

Several potential limitations need to be addressed. First, the small sample and open-label design are major drawbacks of our study. We attempted to minimize the inherent limitations in an open-label design with blinded IVUS measurements. Second, because this trial included only statin-naive patients with mild coronary atherosclerotic plaques, our findings cannot be extrapolated to patients with significant coronary artery disease or those administered statins.

1. Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1781–1790.
2. Schoenhagen P, Brown BG, Schoenhagen P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071–1080.
3. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;295:1556–1565.
4. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011;365:2078–2087.
5. Liao JK, Laufs U. Pleiotropic effects of statins. *Annu Rev Pharmacol Toxicol* 2005;45:89–118.
6. Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, Yamaguchi T, Matsuzaki M; COSMOS Investigators. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Circ J* 2009;73:2110–2117.
7. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA, Blasetto JW; STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol* 2003;92:152–160.
8. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–2207.
9. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, Daida H. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. *Circulation* 2004;110:1061–1068.
10. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:2292–2300.
11. Riccioni G, Cipollone F, Santovito D, Scotti L, D'Orazio N, Mezzetti A, Bucciarelli T. Effect of 2-year treatment with low-dose rosuvastatin on intima-media thickness in hypercholesterolemic subjects with asymptomatic carotid artery disease. *Expert Opin Pharmacother* 2011;12:2599–2604.
12. Cuchel M, Rader DJ. Macrophage reverse cholesterol transport: key to the regression of atherosclerosis? *Circulation* 2006;113:2540–2555.
13. Lee CW, Park CS, Hwang I, Kim Y, Park DW, Kang SJ, Lee SH, Kim YH, Park SW, Park SJ. Expression of HMG-CoA reductase in human coronary atherosclerotic plaques and relationship to plaque destabilisation. *Heart* 2011;97:715–720.
14. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–1164.
15. McTaggart F. Comparative pharmacology of rosuvastatin. *Atheroscler Suppl* 2003;4:9–14.
16. Skazik C, Heise R, Bostanci O, Paul N, Denecke B, Joussen S, Kiehl K, Merk HF, Zwadlo-Klarwasser G, Baron JM. Differential expression of influx and efflux transport proteins in human antigen presenting cells. *Exp Dermatol* 2008;17:739–747.
17. Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, Collins R; SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N Engl J Med* 2008;359:789–799.