Materials and Methods

Study population
This study was a prospective, randomized, open-labeled, 2 × 2 factorial designed single-center trial. Each patient was assigned to a group based on the statin and type of DES (first-generation sirolimus-eluting stent [SES, Cypher; Cordis, Miami Lake, FL] vs. everolimus-eluting stent [EES, Xience; Abbott Vascular, Santa Clara, CA]). A total of 60 patients who fulfilled the inclusion criteria and were in agreement on serial OCT follow-up were included in this trial between August 2011 and January 2013. Each patient was randomly assigned into either the high-dose statin therapy (atorvastatin 40 mg) or low-dose statin therapy (pravastatin 20 mg) group (1) (ClinicalTrials.gov Identifier: NCT01856374). Detailed information regarding the inclusion and exclusion criteria of this study were previously reported (2). Serial OCT examinations were performed at three time points, including post-procedure, and at the 3- and 12-month post-procedure follow-ups. This randomized study was approved by our Institutional Review Board, and written informed consent was obtained from all enrolled patients.

Randomization and study procedures
Study patients fulfilling the enrollment criteria were randomly assigned in a 1:1 ratio to receive either atorvastatin 40 mg (n=29) or pravastatin 20 mg (n=31), and either SES (n=30) vs. EES (n=30) (2 × 2 design) by a concealed interactive web-based response system. To preserve the balance between the two DES groups, stratified randomization was performed according to the estimated length and diameter of the implanted DES. All patients received at least 75 mg of aspirin and a loading dose of 300 mg of clopidogrel at least 12 hours before percutaneous coronary intervention. Unfractionated heparin was administered to maintain an activated clotting time of >250 seconds. All percutaneous coronary intervention procedures were performed according to current standard techniques. Post-procedure treatment included a 12-month prescription for dual antiplatelet therapy with 100 mg of aspirin and 75 mg of clopidogrel daily.

Quantitative coronary angiography
Quantitative coronary angiography analysis was performed before and after stent implantation and at the 3- and 12-month follow-ups using an off-line quantitative coronary angiographic system (CAAS system; Pie Medical Instruments, Maastricht, Netherlands) in an independent core laboratory (Cardiovascular Research Center, Seoul, Korea). Using the guiding catheter for magnification-calibration, the reference vessel diameter and minimum luminal diameter were measured from the diastolic frames in a single, matched view showing the smallest minimum luminal diameter. Late loss was defined as the difference between the post-procedure and follow-up minimal luminal diameter. Angiographic restenosis was defined as stenosis ≥50% in diameter inside the stent or within a 5-mm segment proximal or distal to the stent at follow-up.

OCT imaging and analysis
Patients were examined immediately post-procedure and again at 3- and 12-months post-procedure; pre-intervention OCT examination was not mandatory. Imaging of the target lesion was performed using a frequency-domain OCT system (C7-XR OCT imaging system; LightLab Imaging, Inc./St. Jude Medical, St. Paul, MN). The OCT cross-sectional images were generated at a rotational speed of 100 frames/s, while the fiber was withdrawn at a speed of 20 mm/s within the stationary imaging sheath. All OCT images were analyzed at the core laboratory (Cardiovascular Research Center, Seoul, Korea) by analysts who were blinded to patient and procedural information.
Cross-sectional OCT images were analyzed at 0.2-mm intervals. The stent and luminal cross-sectional areas (CSAs) were measured, and neointimal hyperplasia (NIH) CSA was calculated as the stent CSA minus luminal CSA. The NIH thickness was measured using the distance between the endoluminal surface of the neointima and the strut, and an uncovered strut was defined as having an NIH thickness of 0 µm (3,4). A malapposed strut was defined as a strut that had detached from the vessel wall by ≥100 µm in EES or ≥160 µm in SES (3,5). The percentage of uncovered or malapposed struts was calculated as the respective ratio of uncovered or malapposed struts to the total struts in all OCT cross sections. Stent malapposition was defined as the presence of any malapposed struts, and late-acquired malapposition was defined as the newly developed malapposition in the matching frames between post-procedure and follow-up OCT images (6). For evaluating malapposition magnitude, the total extra-stent luminal volume, maximum extra-stent luminal CSA, and the maximum distance between the malapposed strut and vessel wall were measured. Intrastent thrombi were defined as an irregular mass protruding into the lumen that was ≥250 µm at its thickest point (7). For serial comparisons, the total stent length was measured at baseline and at the 3- and 12-month follow-ups; unchanged stent length was confirmed in all lesions (8, 9). Cross-sectional OCT images taken at the 3- and 12-month follow-ups were meticulously matched using the distance from the stent edge and landmarks such as side branches, ostium location, and calcified plaques. The changes (Δ) of OCT parameters were calculated as the values at the 12-month follow-up minus the values at the 3-month follow-up. OCT images were all measured at an independent OCT core laboratory under regular quality control. The inter- and intra-observer variabilities in OCT-measured distances and areas were determined in a prior study (8). In addition, we randomly selected 40 cross-sections at 3 months and 12 months and measured two times in same analyst with different time points and 2 different analysts.

**Study endpoints and statistical analysis**

The primary endpoint was the percentage of uncovered struts for atorvastatin- and pravastatin-treated patients in 12-month follow-up OCT images. The secondary endpoint was the percentage of uncovered struts for atorvastatin- and pravastatin-treated patients in 3-month follow-up OCT images, and the percentage Δ of uncovered struts in the 3-month versus 12-month follow-up samples. Clinical follow-up was performed at 1, 3, 6, 9, and 12 months after percutaneous coronary intervention. Laboratory evaluations included high sensitivity C-reactive protein, total cholesterol, triglycerides, and high-density lipoprotein and LDL cholesterol.

Statistical analysis was performed with the Statistical Analysis System software (SAS v. 9.1.3; SAS Institute, Cary, NC) and R version 3.12 (R Development Core Team, Vienna, Austria, http://www.R-project.org). Categorical data were presented as numbers and percentages and compared with chi-squared statistics or Fisher’s exact test as appropriate. Continuous data were presented as the mean±standard deviation and compared with Student’s t-test or paired t-test. If data distributions were skewed, medians with interquartile range were provided, and a non-parametric test was used for comparison. Cross-sectional and strut-level data were analyzed with the hierarchical multilevel regression model to handle the clustering problem under each individual patient/lesion level. Specifically, the patient and lesion information were incorporated as random effect components using the lme4 package with R (http://cran.r-project.org/web/packages/lme4/index.html) (10). Repeated-measure analysis of variance was also performed to compare the groups along with the time intervals. Inter- and intra-observer agreements in the measurements of NIH thickness and uncovered struts were assessed using the intra-class correlation coefficient (ICC) and Cohen’s k, respectively, with 40 randomly selected cross-sectional images by two independent readers and by the same reader at two separate time points. A two-sided p-value less than 0.05 was considered statistically significant.
References