rug-eluting stents (DES) are widely used to treat coronary artery disease and have successfully decreased the rate of restenosis and the need for repeat revascularization compared with bare metal stents (BMS). However, the antiproliferative drugs, sirolimus and paclitaxel, that are released from the polymer also delay vessel healing and limit re-endothelialization, which, in turn, may cause late stent thrombosis (LST).

Although the annual incidence of LST is only 0.4–0.6%, the result is mostly acute myocardial infarction and sudden death with a reported mortality of 15.6–45%,

Conclusions: Atorvastatin pretreatment can accelerate both neointimal coverage and re-endothelialization after SES implantation, which may be mediated by the mobilization of EPC and enhancement of the endothelial function of the neointima. (*Circ J* 2012; 76: 2561–2571)

Key Words: Drug-eluting stents; Endothelial progenitor cells; Late stent thrombosis; Optical coherence tomography; Statins

Received April 9, 2012; revised manuscript received June 5, 2012; accepted July 9, 2012; released online August 8, 2012 Time for primary review: 27 days

Department of Cardiology, State Key Laboratory of Cardiovascular Disease (T.-J.W., Y.-J.Y., Q.Z., C.J.), Department of Catheterization Laboratory (B.X.), and Experimental Animal Center (Y. Tang, Y. Tian), Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People’s Republic of China; and Cardiovascular Research Foundation, New York, NY (G.S.M.), USA

Mailing address: Yue-Jin Yang, MD, PhD, FACC, Professor and Vice President, Centre for Coronary Heart Disease, Department of Cardiology, State Key Laboratory of Cardiovascular Disease, FuWai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishi Rd, Xicheng District, Beijing 100037, People’s Republic of China. E-mail: yangyjfw@yahoo.com.cn


All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
ment. Some previous studies have suggested that statins may assist re-endothelialization by enhancing the proliferation and migration of both mature endothelial cells and endothelial progenitor cells (EPCs). However, other research shows inconsistent results and the beneficial effects of statins on re-endothelialization after stent implantation are still controversial.

With the development of newer intracoronary imaging techniques, the percentage of uncovered struts now can be evaluated using optical coherence tomography (OCT), which has an extremely high resolution of approximately 10–15 μm. However, OCT cannot differentiate whether endothelial cells exist above the neointima, so in the present study we compared the results from OCT and histopathology to verify the relationship between neointimal coverage and re-endothelialization, and to assess whether atorvastatin can improve the delayed vessel healing after DES implantation.

**Methods**

**Porcine Model of Stent Implantation**

Animal experiments were conducted at the Animal Experiment Center of FuWai Hospital (Beijing, China) in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The study protocol was reviewed and approved by the Care of Experimental Animals Committee of FuWai Hospital, Peking Union Medical College, and the Chinese Academy of Medical Sciences.

The protocol involved randomly dividing 45 healthy Chinese minipigs (10 months old, 20–25 kg) into 3 groups: BMS (n=15), sirolimus-eluting stent (SES; n=15), and SES plus atorvastatin pretreatment (SES+ator; n=15). Each minipig was given 300 mg clopidogrel and 300 mg aspirin 1 night before stent implantation and 75 mg/day aspirin until death. Minipigs in the SES+ator group were given a 50-mg atorvastatin loading dose 12 h before stent implantation and 20 mg daily after stent implantation (The dose used in minipigs was equal to that used in acute coronary syndrome patients in the ARMYDA-ACS trial).

After being anesthetized, either a BMS (Multi-link Vision 2.75×15 mm, Abbott Vascular, Santa Clara, CA, USA) or a SES (Firebird-2 2.75×18 mm stent structure: cobalt-chromium alloy stent platform with a styrene-butylstyrene copolymer; the dose of sirolimus: 9 μg/mm; drug release kinetics: 90% of the drug was eluted from the stent within 30 days of implantation, MicroPort, Shanghai, China) was deployed in the right coronary artery using conventional techniques. The guiding catheter was utilized as a reference to obtain a 1:1 stent-to-artery ratio compared with the baseline vessel diameter.

**OCT Imaging and Analysis**

OCT examination was performed immediately after stent deployment and at 7 days (n=5 in each group), 14 days (n=5 in each group), and 28 days (n=5 in each group) thereafter. This study used a time-domain OCT (TD-OCT) system (M2 Cardiology Imaging System, Light Lab Imaging, Westford, MA, USA), an over-the-wire-type occlusion balloon catheter (Helios, Avantec Vascular Corp, Sunnyvale, CA, USA), and a 0.016-inch OCT imaging wire (ImageWire, Light Lab Imaging). As previously described, the imaging wire was passed through the occlusion balloon and advanced to the distal end of the stent, the occlusion balloon was positioned at the proximal end of the stent and inflated to 0.4–0.6 atm, and lactated Ringer’s solution or saline was injected into the coronary artery at 1 ml/s to remove blood from the field of view while imaging. OCT imaging was performed during motorized imaging wire withdrawal at 2 mm/s. Continuous images were acquired at 20 frames/s and stored digitally for subsequent analysis.

Cross-sectional OCT images were analyzed at 1-mm intervals (every 10 frames) and strut malapposition, uncovered struts, neointimal hyperplasia (NIH) thickness, lumen area, and stent

<table>
<thead>
<tr>
<th>Table 1. Optical Coherence Tomography Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>SES</td>
</tr>
<tr>
<td>SES+ator</td>
</tr>
<tr>
<td><strong>Mean NIH thickness (μm)</strong></td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>SES</td>
</tr>
<tr>
<td>SES+ator</td>
</tr>
<tr>
<td><strong>Mean lumen area (mm²)</strong></td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>SES</td>
</tr>
<tr>
<td>SES+ator</td>
</tr>
</tbody>
</table>

*P<0.05 compared with BMS; †P<0.05 compared with SES at the same time point.

ator, atorvastatin; BMS, bare metal stent; SES, sirolimus-eluting stent; NIH, neointimal hyperplasia; PCI, percutaneous coronary intervention.
Figure 1. (a) OCT measurements of neointimal coverage and thickness. (A–L) Typical cross-section images of stent coverage in the 3 stent groups immediately after PCI and on days 7, 14, and 28. (C, G, K) Stent coverage was almost complete on day 14 in the BMS group, but incomplete on day 14 for the DES. The red asterisk represents malapposed struts and the red arrow represents uncovered struts. The bar graphs on the right show the quantitative analysis of the uncovered strut ratio (M), ratio of cross-section with more than 30% uncovered struts (N) and NIH thickness (O) at the 3 time points. (b) Histological sections of right coronary arteries stained with H&E on days 7, 14 and 28. There is obvious neointimal hyperplasia in the BMS group (C), uneven neointimal coverage with persistent uncovered struts in the SES group (F), and optimal vessel healing without neointimal hyperplasia in the SES+ator group (I) on day 28 (×40). Arrows point to uncovered struts. *P<0.05 compared with the BMS group; †P<0.05 compared with the SES group. BMS, bare metal stent; SES, sirolimus-eluting stent; OCT, optical coherence tomography; NIH, neointimal hyperplasia.
area were assessed. Strut malapposition was defined as the distance from the center reflection of the strut surface to the adjacent vessel wall >140 μm in SES and >90 μm in BMS (strut thickness of Firebird-2 [130 μm] or Multi-link Vision [81 μm] + OCT resolution of 10 μm). NIH thickness was measured along a line perpendicular to the neointima and strut. An uncovered strut was defined as an NIH thickness of 0. The ratio of uncovered to total struts per stent was then calculated.

### Scanning Electron Microscopy (SEM) Image Acquisition and Analysis

The animals were euthanased at 7 days (n=5 for each group), 14 days (n=5 for each group), and 28 days (n=5 for each group) after OCT imaging. The right coronary artery was dissected from the heart and perfused with lactated Ringer’s solution at 80–100 mmHg for 30 min, and the tissue was fixed with 10% buffered formalin. The right coronary artery was then cut longitudinally and prepared for SEM as described previously. En face SEM images were acquired at low power (>25 magnification) to reflect the overall neointimal coverage of the stents and at high power (>500 magnification) to directly identify the composition of the tissue covering the surfaces of the stents. Endothelial cells were identified as sheets of closely connected monolayer cells with a spindle or polygonal shape, whereas platelets were identified as individual cells, 1–2 μm in size, with an irregular discoid appearance and adhering to the surface of the stent or neointima. The percentage of endothelial covered area was calculated. The number of platelets adhering to the neointima completely covered by endothelial cells was counted in 10 random high-power fields of each stent (3 fields at the proximal segment, 4 at the middle segment, and 3 at the distal segment) using morphometry software (Image-Pro Plus, Media Cybernetics, MD, USA).

### Table 2. Histopathologic Measurements

<table>
<thead>
<tr>
<th>Group</th>
<th>Lumen area (mm²)</th>
<th>IEL (mm²)</th>
<th>EEL (mm²)</th>
<th>Neointimal area (mm²)</th>
<th>Injury score</th>
<th>Fibrin score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14-day</td>
<td>28-day</td>
<td>14-day</td>
<td>28-day</td>
<td>14-day</td>
<td>28-day</td>
</tr>
<tr>
<td>BMS</td>
<td>5.7±0.3</td>
<td>2.7±0.3</td>
<td>6.8±0.4</td>
<td>6.4±0.5</td>
<td>8.0±0.5</td>
<td>7.8±0.6</td>
</tr>
<tr>
<td>SES</td>
<td>6.1±0.5</td>
<td>4.2±1.6*</td>
<td>6.3±0.5</td>
<td>5.9±1.0</td>
<td>8.0±0.7</td>
<td>7.5±0.8</td>
</tr>
<tr>
<td>SES+ator</td>
<td>5.8±1.2</td>
<td>4.2±1.4*</td>
<td>6.3±1.0</td>
<td>5.7±0.9</td>
<td>7.6±0.9</td>
<td>7.5±0.7</td>
</tr>
</tbody>
</table>

*P<0.05 compared with the BMS group. EEL, external elastic lamina; IEL, internal elastic lamina. Other abbreviations as in Table 1.

### Figure 2

Scanning electron micrographs of stent coverage in the 3 stent groups on days 7, 14, and 28. BMS, bare metal stent; SES, sirolimus-eluting stent.
Pathological Assessment and Morphological Analysis
The right coronary artery segments containing the stents were dissected from the heart and fixed in 10% buffered formalin overnight before being embedded in methyl methacrylate. Serial 5-μm sections were cut at 2–3-mm intervals and stained with hematoxylin-eosin (H&E). The percentage of stent coverage was calculated. Histopathologic measurement of the injury score, internal and external elastic lamina areas, and neointimal area and thickness were quantified at the proximal, middle, and distant segments of each stent. Fibrin was scored from 0 to 4 (0=no fibrin present, 1=very weak present, 2=weak present, 3=moderate present, 4=intense present) for staining intensity and distribution.21 Endothelium was identified by immunofluorescent staining of von Willebrand factor (vWF,
Peripheral Blood EPC Count
A volume of 20 ml of peripheral blood was obtained at pre-
procedure and follow-up in the SES and SES + ator groups.
Mononuclear cells were isolated by density gradient centrifuga-
tion using Percoll (1.077 g/ml; GE Healthcare, Sweden) and
incubated with phycoerythrin (PE)-labeled monoclonal anti-
bodies against porcine KDR (RD Systems China Co, Shanghai,
China) and fluorescein isothiocyanate-labeled monoclonal an-
tibodies against porcine CD34 (Abcam, Hong Kong, China).
Isotype identical antibodies served as controls.
After incuba-
tion for 45 min in the dark, cells were washed twice with phos-
phate-buffered saline and fixed in 4% paraformaldehyde. Dual-
positive cells within the lymphocyte gate were judged as EPCs,
and the percentage of EPCs was counted using flow cytome-
try.

Statistical Analysis
All data are expressed as mean±SE, and were analyzed using
SPSS software (version 15.0, Chicago, IL, USA). Differences
among groups were tested by 1-way ANOVA. A value of
P<0.05 was considered to be statistically significant.

Results
All stents remained angiographically patent at 7, 14 and 28
days without evidence of stent thrombosis. No thrombus was
detected in any animal using OCT during the 28-day follow-
up.

Stent Coverage and Neointimal Thickness
OCT was successfully performed in all 45 stents and overall,
828 cross-sections and 6901 struts were analyzed (Table 1).
The percentage of malapposed struts immediately after stent
deployment was very low, with no significant difference among
the 3 groups (BMS 6.0±2.5%, SES 3.5±4.9%, SES + ator 5.3±
2.6%, P=NS).

OCT showed that stent coverage was significantly delayed
in the SES group, which had more uncovered struts compared
with the BMS group. However, the SES + ator group had fewer
uncovered struts than did the SES group on days 7 (P<0.01)
and 14 (P<0.01), but not on day 28 (P=0.41) (Figure 1a-M).
The number of cross-sections with >30% uncovered struts, an
index of the risk of thrombus formation, showed a trend simi-
lar to the rate of uncovered struts (Figure 1a-N).

However, the BMS group had a significantly thicker neo-
intima and more severe lumen restenosis on day 28 than did the
other 2 groups (Figures 1a-D,1a-H,1a-L,1a-O). Although
the SES + ator group had a trend toward a thicker neointima
covering the struts, there were no significant differences in
NIH thickness, stent area, or lumen area between the SES and
SES + ator groups (Table 1).

The histopathologic measurements are shown in Table 2.
More severely decreased lumen area and increased neointimal
area in the BMS group were in accordance with the results of
OCT. No significant difference was found between the SES
and SES + ator groups. The injury score was quite low in the 3
groups. There was a trend toward a higher fibrin score in the
SES and SES + ator groups compared with the BMS group
without significant difference.

Neointimal Coverage Compared With Re-Endothelialization
The histological sections stained by H&E showed a similar
result for neointimal coverage as did OCT (Figure 1b). Neo-
intima on day 7 was mainly composed of fibrin, inflammatory
cells, and organized thrombus in the 3 groups. SEM also showed
that neointima formation was delayed in the SES group com-
pared with the BMS group on days 7, 14, and 28 (Figure 2).
A few bare struts, partially covered by fibrin, were still visible in the SES group on day 28 (Figure 2F).

However, when comparing the results of neointimal coverage from OCT and pathology with the endothelium coverage from SEM and pathology, we found that the re-endothelialization of SES was more severely delayed than neointimal coverage, especially at 7 and 14 days (Figure 3). Endothelial cells did not always accompany neointima formation. Although OCT and pathology showed a similar degree of stent coverage among the 3 groups on day 28, there was still a large region of neointima without endothelial cell coverage in the SES group. However, atorvastatin treatment increased re-endothelialization

Figure 5. Platelet adhesion on endothelium of neointima in the 3 stent groups on days 7, 14, and 28. (A) Neointima always shows partial re-endothelialization and platelets prefer to adhere to the region without endothelial cells (×500). (B) Bar graph showing that the number of adhering platelets decreased over time in the 3 groups. Compared with the BMS group, the SES group showed more platelet adhesion on days 7, 14, and 28. The SES + ator group showed fewer platelets than did the SES group. *P<0.05 compared with the BMS group; †P<0.05 compared with the SES group. BMS, bare metal stent; EC, endothelial cell; PLT, platelet; SES, sirolimus-eluting stent.
and the SES+ator group had a higher percentage of endothelial covered area than did the SES group (P<0.05) (Figure 3).

Endothelial Function and Platelet Adhesion

The results of immunofluorescent staining confirmed that vWF and eNOS expression were decreased in the neointima of the SES group compared with the BMS group. However, atorvastatin therapy improved endothelial function in the SES+ator group by increasing the expression of vWF and eNOS (Figure 4). From the high-power image of the local neointima (panel insets in Figure 5A, ×500 magnification), we found that, compared with the neointima covered by endothelium, platelets mostly adhered to the bare site of the stent and to the neointima without endothelial coverage. The degree of platelet adhesion to endothelium per unit area was significantly higher in the SES group than in the BMS group on day 7 (213.9±58.0 vs. 88.0±24.2, P<0.01), day 14 (199.7±10.9 vs. 105.3±12.7, P<0.01), and day 28 (125.1±17.0 vs. 33.0±10.6, P<0.01). However, the SES+ator group had fewer platelets adherent to the endothelium compared to the SES group at all 3 time points (P<0.01 for all comparisons). This result indicated that endothelial cell function improved with atorvastatin therapy. There

---

**Figure 6.** EPC mobilization in the SES and SES+ator groups on days 7, 14, and 28. (A) EPCs identified as KDR/CD34 double-positive cells in the upper right quarter of each image. (B) Bar graph showing the percentage of EPCs among peripheral blood MNCs at different time points. EPCs increase 2–3-fold in both groups on day 7 and gradually decreased to baseline on day 28. However, the SES+ator group had greater EPC mobilization on day 7 compared with the SES group and it even lasted to day 14. EPCs, endothelial progenitor cells; MNCs, mononuclear cells; SES, sirolimus-eluting stent.
was also a trend toward decreased platelet adhesion on endothelial cells over time (Figure 5B).

**EPC Mobilization in Peripheral Blood Detected by Flow Cytometry**

In the present study EPCs were identified as CD34/KDR double-positive cells (Figure 6A). The number of EPCs in the SES and SES-ator group was checked to verify the effect of atorvastatin on EPC mobilization. The baseline level of circulating EPCs before percutaneous coronary intervention (PCI) was not different between the 2 groups (0.07±0.02%/ vs. 0.06±0.02%, P=0.75). The number of EPCs in peripheral blood increased on day 7 and decreased to baseline on day 28 in both groups. However, on day 7 the SES-ator group had more mobilized EPCs than did the SES group (0.21±0.02%/ vs. 0.11±0.03%, P=0.02). The trend remained apparent on day 14 (0.14±0.05% vs. 0.09±0.02%, P=0.20), although the effect of atorvastatin on EPC mobilization decreased over time, and the 28-day results showed no significant differences between the 2 groups (Figure 6B).

**Discussion**

The results of this study in a porcine model demonstrated that re-endothelialization was not in accordance with neointimal growth after SES deployment and a diagnostic gap between OCT and pathology for re-endothelialization was found. However, atorvastatin treatment significantly (1) accelerated neointimal coverage after SES implantation in association with significant EPC mobilization, and (2) increased re-endothelialization and improved endothelial cell function above the neointima. These new findings showed that stent coverage evaluated by OCT may have a diagnostic discrepancy with re-endothelialization of the coronary artery. Atorvastatin pretreatment improved the delayed vessel healing after SES implantation in porcine coronary arteries and may help to explain the beneficial effect of atorvastatin besides lipid-lowering.

**LST and Vessel Healing**

Previous data using OCT have shown incomplete neointimal coverage a long time after SES implantation. Compared with BMS, delayed neointimal coverage was also verified in our porcine model. Persistently uncovered stent struts are a symbol of delayed neointima formation and extend the window of time in which the stent is prone to thrombosis.

Furthermore, the risk of LST increases as the number of uncovered struts increases and becomes extraordinarily high when the ratio of uncovered to total struts per section is more than 30%. Compared with paclitaxel-eluting stents and everolimus-eluting stents, SES has a higher incidence of uncovered struts increases and becomes extraordinarily high when the ratio of uncovered to total struts per section is more than 30%. Compared with paclitaxel-eluting stents and everolimus-eluting stents, SES has a higher incidence of uncovered struts and intracoronary mural thrombus or stent thrombosis.

However, vessel healing after stent implantation is a complex process involving inflammatory cells, smooth muscle cells (SMC), endothelial cells, and progenitor cells. A previous study by Ishigami et al showed thrombus on stent struts that were completely covered by neointimal tissue, implying that the neointima may be lined with dysfunctional endothelial cells or even without endothelial cells. In the present study, by comparing the results of neointimal coverage and endothelium coverage, we found that re-endothelialization was more severely delayed than neointimal coverage. In addition, OCT could not distinguish the endothelial cells above the neointima, which caused a discrepancy between the ratio of neointimal coverage revealed by OCT and the actual re-endothelialization on the stent. So the neointima covering the stents may not be accompanied by endothelium, and, therefore, cannot exert a protective action against thrombus.

**Vessel Healing and Statins**

Statins display a favorable effect on endothelial cell proliferation and migration, as well as a profound inhibitory effect on SMC proliferation, making them a potentially valuable drug in vessel healing after DES implantation. However, other research has demonstrated no beneficial effect of statin therapy on stent coverage after DES implantation in porcine coronary arteries. Cho et al found that combined therapy with ezetimibe and simvastatin further inhibited NIH in DES with no benefit for stent coverage after 28 days. Neointima grows much more rapidly in the porcine model than in humans. In the present study, neointimal coverage was almost complete in all 3 groups after 28 days. The percentage of uncovered stent struts on day 28 in the SES group without atorvastatin pretreatment was similar to that in humans after 12 months. Therefore, we chose earlier time points (ie, days 7 and 14) in order to monitor the effect of atorvastatin on neointimal coverage. The presented OCT results on days 7 and 14 showed a significant decrease in uncovered struts and cross-sections with >30% uncovered stent struts in the atorvastatin treatment group compared to SES without atorvastatin.

**Improved Endothelial Cell Function With Atorvastatin**

Besides neointimal coverage, impaired endothelial function is also considered to be an important cause of LST. Previous studies have revealed that sirolimus can damage the normal function of endothelial cells. Fuke et al and Togni et al showed that SES implantation impaired the exercise- and acetylcholine-induced endothelium-dependent vasodilatory function at the proximal and distal sites of the stent compared with BMS. Fukuda et al reported that sirolimus could impair the function of human umbilical vein endothelial cells by inhibiting eNOS expression and increasing the expression of plasminogen activator inhibitor-I.

By contrast, statins can induce EPCs to differentiate into mature endothelial cells through the activation of eNOS by AMPK and promote the function of endothelial cells by activating the PI3K/Akt pathway and increasing the activity of eNOS and the production of NO. NO is important for maintaining the normal function of endothelial cells. Reduced NO production can lead to platelet aggregation, accelerated leukocyte adhesion, and increased vascular SMC migration and proliferation. In the present study, SEM illustrated that neointima covered by endothelial cells had less platelet adhesion compared with neointima consisting of fibrin and organized thrombus. In comparison to the SES group, platelet adhesion on endothelium was ameliorated by atorvastatin treatment. The increased expression of eNOS also reflected the improved function of endothelial cells.

**EPCs Mobilization and Vessel Healing**

A number of studies have demonstrated that EPCs play an important role in vessel healing. When vessels are injured by trauma, degeneration, or atherosclerotic lesions, EPCs can be mobilized from bone marrow, migrate to the site of injury, and differentiate into mature endothelial cells to repair injured tissue. In addition, Banerjee et al showed that EPC mobilization could be triggered 12 h after PCI as a result of focal coronary endothelial injury caused by stent implantation. EPC mobilization was also found in the present study on day 7. Previous studies have shown that atorvastatin can accelerate the
proliferation and migration of EPCs. In the present study, EPC mobilization in peripheral blood was more sharply enhanced in the atorvastatin treatment group than in the SES group without atorvastatin treatment and remained at a high level until day 14. This increased level of EPCs in peripheral blood may have accelerated neointimal coverage and re-endothelialization after SES implantation. The present results were also comparable to those from a randomized control study showing that 3 weeks of atorvastatin therapy increased circulating EPCs 4-fold after cardiopulmonary bypass surgery. In addition, a prospective study showed that 40mg/day of atorvastatin for 4 weeks was associated with an approximately 3-fold increase in EPCs in patients with stable coronary artery disease.

**Study Limitations**

First, the exact mechanism of LST is complicated, multifactorial, and influenced by factors not mentioned in this study. The science advisory committees of the ACC/AHA/SCAI/ACS/ADA have reported other clinical risks, such as acute myocardial infarction, stent deployment overlying a large lipid burden with a thin fibrous cap, and overlapped stents, that might preclude growth of neointima. Therefore, it may be difficult to apply the present findings directly to complex clinical situations. However, this research still provides a novel way of explaining the beneficial effect of stent pretreatment before PCI in the ARMYDA trials. Second, different types of BMS and SES were used in this study, and the strut thickness and platform could affect the vessel healing process. A third limitation was that no stent thrombosis was found in this study. This may have been because of the low incidence of LST, limited number of animals, or the dual antiplatelet therapy of clopidogrel and aspirin used after stent implantation. Finally, the present findings showed that atorvastatin accelerated the process of neointima formation in normal arteries. Stent deployment in atherosclerotic arteries of hypercholesterolemic swine would be a more suitable model. However, the preclinical studies of the new types of stents also chose healthy animal model for research, so our study could still provide new insight to evaluating the vessel healing process after DES implantation.

In conclusion, from the results of OCT, pathology, and SEM, we found that re-endothelialization was more severely delayed than neointimal coverage after DES implantation. The discrepancy between the neointimal coverage evaluated by OCT and the actual re-endothelialization after DES implantation should be a concern for future studies. On the other hand, atorvastatin can accelerate the vessel healing process after SES implantation by increasing both neointimal coverage and re-endothelialization of the stent. If validated, this could decrease the window of time for susceptibility to LST and shorten the time course of dual antiplatelet drug therapy, as well as their side effects.

**Acknowledgments**

This study was supported by grants from Clinical Key Project of the Ministry of Health of China, National Natural Science Foundation of China [Grant No. 81070169, 81170129 to Y. J. Yang], China Health and Medical Development Foundation [2008-zhfj2 and 2011-H25 to Y. J. Yang], China Health and Ministry of Health of China, National Natural Science Foundation of China [Grant No. 20100470010 to H. Wang].

**References**


