Biological effect of microengineered grooved stents on strut healing: a randomised OCT-based comparative study in humans

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ABSTRACT

Objective To evaluate the biological effect of microengineered stent grooves (MSG) on early strut healing in humans by performing optical coherence tomography (OCT) analysis 3 weeks following the implantation.

Background In the experimental setting, MSG accelerate endothelial cell migration and reduce neointimal proliferation compared with bare metal stent (BMS).

Methods A total of 37 patients undergoing percutaneous coronary intervention with de novo coronary lesions were randomly assigned to either MSG (n=19) or an identical BMS controls (n=18). All patients underwent OCT imaging at 3 weeks. A total of 7959 struts were included in the final analysis.

Results At 3 weeks following stent implantation, almost all struts analysed (~97%) had evidence of tissue coverage. The percentage of partially covered struts was comparable between both groups. However, the percentage of fully embedded struts was higher in the BMS group (81.22%, 49.75–95.52) compared with the MSG group (74.21%, 58.85–86.38). The stent-level analysis demonstrated reduction in neointimal formation (neointimal hyperplasia area and volume reduction of ~14% and ~19%, respectively) in the MSG versus the BMS group. In the strut-level analysis, an even greater reduction (~22% in neointimal thickness) was seen in the MSG group. Layered neointimal was present in ~6% of the OCT frames in the BMS group while it was not present in the MSG group.

Conclusions MSG induced a more homogeneous and predictable pattern of surface healing in the early stages following stent implantation. The biological effect of MSG on stent healing has the potential to improve the safety profile of current generation drug-eluting stents.

Classifications BMS, OCT, clinical trials.

INTRODUCTION

Drug-eluting stent (DES) failure is a multifactorial clinical phenomenon that continues to occur over time.1 Several studies have described delayed healing and neointimal-sclerosis as the most important biological mechanisms responsible for this condition.2

In the experimental setting, accelerated strut endothelialisation results in the more rapid development of a lower and more organised neointimal response even in the absence of antiproliferative drugs.3 Then, technologies capable of accelerating strut endothelialisation have the potential to improve the safety profile of current generation metallic DES. In addition, to the fact that the grooves can be applied to different surfaces, it has the potential to improve the healing profile of thicker strut devices such as biodegradable scaffolds.
neointimal proliferation compared with stents exposing flat metal surfaces. In this study, we aimed to test the safety and healing profile of MSG in humans by comparing the patterns of stent healing of identical bare metal stent (BMS) exposing two different luminal surfaces (MSG vs flat) using optical coherence tomography (OCT) analysis 3 weeks following stent implantation.

METHODS

Stent system description

All devices used in this study were commercially available Multi-Link Vision stents (Abbott Vascular, Santa Clara, CA). The stents are manufactured using medical grade L-605 Cobalt Chromium (strut thickness of ~80 μm). Stents were available in 18 and 23 mm lengths and 2.75 and 3.0 mm diameters. The MSG technology was applied on the luminal surface of the stents by Palmaz Scientific (Fremont, CA). Final manufacturing process was performed by Creganna Medical (Galway, Ireland). Device labels were blinded to keep the identity of both devices confidential, allowing true operator blinding through the implantation procedure.

Microgroove stent technology

The current standard in stent technology relies on achieving a smooth flat stent surface. Over the years, different surface modification technologies have sought to influence cell colonisation of the stent inner surface by engineering defined microscopic features such as parallel microengineered grooves (figure 1). At the early stages of development of this technology, mechanical grooving was achieved by the use of calibrated abrasive materials. Later on, microgroove development based on laser technology allowed to establish the ideal boundary conditions for endothelial cell (EC) migration speed and groove configuration, therefore aiding optimisation of engineering parameters. Recent technology developments using photolithographic techniques have achieved a markedly improved resolution in the development of the microgroove patterns. Accuracy of the manufacturing process has improved over time and allowed the development of groove features in the micron range. The specific features of the MSG have been derived from studies assessing EC response to edge, shape and depth definition. A measurable increase in the cellular response has been seen, demonstrating a peculiar sensitivity of the EC to defined microscopic features. This cellular sensitivity is more dependent on the microgroove geometry rather than the material used (metals and polymers, data not shown). Patterns inscribed on natural alloys are less regular as those obtained in vapour-deposited alloys. The uniform size, shape and orientation of crystals as well as markedly decreased intergranular inclusions in the latter allow for higher definition patterns (figure 2).

Study design

This study was performed in compliance with the ethical principles of the Helsinki's Declaration (59th WMA General Assembly, Seoul, October 2008). The study was approved by the local hospitals and followed the governmental regulations of the government of Colombia, South America. The study design was a multicentre, prospective, randomised, two-arm study, which enrolled 40 patients randomly assigned (1:1 fashion) to either receive the MSG stent or a BMS control. All patients were scheduled for 3 weeks OCT follow-up and 6 months clinical follow-up. Eligible patients were at least 18 years of age and had a diagnosis of symptomatic ischaemic heart disease due to de novo stenotic lesions in native coronary arteries. Major adverse cardiac events (MACE) were defined as cardiac death, myocardial infarction (MI) or target vessel revascularisation (TVR) and were recorded up to 6 months following device implantation. Stent thrombosis was defined according to the Academic Research Consortium.

Clinical/angiographic inclusion and exclusion criteria

Patients undergoing percutaneous coronary intervention (PCI) due to symptomatic coronary artery disease were included in this study. Patients were excluded if there was evidence of ST-segment elevation MI within the last 72 hours or if the patient (a) had known allergy to cobalt...
chromium, (b) allergy to aspirin or radiographic contract agents, (c) history of bleeding or coagulopathy, (d) was unable to tolerate antiplatelet therapy, (e) had an ejection fraction <45% and (f) presence of systemic infection or underlying diseases.

Angiographic inclusion criteria included single de novo lesions (≥50% stenosis) in a native coronary artery with a reference vessel diameter ≥2.5 mm and ≤3.25 mm and 14–20 mm in length. Exclusion criteria included previous interventional therapy within 15 mm of the borders of the target lesion. In addition, the following lesions were excluded from the study: (a) left main, (b) ostial, (c) bypass graft, (d) side branch ≥2.0 mm in diameter, (e) total vessel occlusion, (f) in-stent restenosis, (g) thrombus presence or (h) need for overlapping stents.

**Stent implantation protocol**

Eligible patients received aspirin (80–325 mg non-enteric coated) starting ≥24 hours prior to procedure and were recommended to receive loading dosages of clopidogrel. During procedure, all patients received standard anticoagulation. Predilation of the target lesion was performed with a balloon ~0.5 mm smaller than the reference vessel diameter. All stents were implanted following standard techniques. After the procedure, all patients were recommended to receive clopidogrel (75 mg daily) to be continued for at least 90 days and aspirin to be continued indefinitely.

**OCT analysis**

All patients underwent OCT evaluation at 3 weeks using the C7-XR imaging system (St. Jude Medical, St. Paul, MN) and a motorised pullback system. Neointimal strut coverage is greatly accelerated in the absence of antiproliferative drugs. Human OCT studies have shown high degrees of stent coverage as early as 4–8 weeks following stent implantation. We chose this early time point because the healing response before complete surface coverage would occur. OCT images were digitally stored and analysed by the Cardiovascular Research Foundation core laboratory which was blinded to the assigned treatment. OCT cross sections (every 1 mm) were selected for quantitative analysis. If a selected frame contained artefacts, the closest artefact-free frame was analysed. Morphometric analysis was performed using standard techniques.

Each analysed strut was classified as either completely or incompletely opposed to the vessel wall and according to whether there was complete tissue coverage or not. The degree of strut coverage adjudication was based on a comprehensive OCT classification. Each stent strut was classified into the following categories: definitely uncovered, uncovered with fibrin, partially covered, covered protruding and covered embedded. A *definitely uncovered strut* was defined as a strut not covered by tissue and both sides appear squared. An *uncovered strut with fibrin* was defined as a strut covered by irregular tissue and both sides appear squared. A *partially covered strut* was defined as a strut covered by tissue partially and at least one side having a smooth shoulder. A *covered protruding strut* was defined as a strut covered by tissue but extending into the lumen. An *embedded strut* was defined as a strut covered by tissue and not interrupting the smooth lumen contour. If the strut was covered with tissue, the tissue thickness was measured from the endoluminal surface of the tissue to the centre of the blooming artefact of the strut. To assess malapposition, we measured the distance from the centre of the stent blooming artefact to the nearby endoluminal surface of the intima. Malapposition was present if the measured distance was greater than the thickness of the stent strut (80 μm). Neointimal tissue was evaluated quantitatively in cross section using an OCT classification, which is based on tissue structure and backscatter.

**Statistical analysis**

Continuous data were presented as mean±SD, if the distributions were skewed, the median with an IQR was provided. For continuous variables with normal distribution, the p-value was derived from Student’s t-test. For continuous variables with non-normal distribution, the p-value comparing treatment groups was derived from the Wilcoxon rank-sum test. For binary variables, p-values from Fisher’s exact test were used when the minimum

### Table 1 Angiographic and procedural features

|                        | BMS (n=18) | MSG (n=19) | p Value |
|------------------------|------------|------------|---------|
| Age                    | 69.43±9.95 | 67.93±9.16 | 0.62    |
| Male gender            | 13 (72.2%) | 9 (47.4%)  | 0.11    |
| Smoking history        | 5 (27.8%)  | 4 (21.1%)  | 0.46    |
| Diabetes mellitus      | 6 (29.4%)  | 5 (26.3%)  | 0.55    |
| Prior PCI              | 3 (16.7%)  | 2 (10.5%)  | 0.47    |
| Target vessel diameter | 2.96±0.16  | 2.9±0.10   | 0.17    |
| % diameter stenosis    | 80.42±8.41 | 82.24±10.18| 0.54    |
| Lesion length          | 15.92±2.62 | 15.83±1.73 | 0.90    |
| Balloon diameter       | 2.36±0.29  | 2.26±0.24  | 0.25    |
| Balloon length         | 15.2±2.62  | 16.43±2.68 | 0.16    |
| Balloon inflation pressure | 9.67±3.9 | 8.95±3.44  | 0.54    |
| Use of 2.75 mm stents  | 7 (36.8%)  | 7 (33.3%)  | 0.82    |
| Use of 23 mm stents    | 5 (26.3%)  | 6 (28.6%)  | 0.87    |
| Moderate–severe tortuosity | 17 (94.4%) | 19 (100%)  | 0.47    |
| Moderate–severe calcification | 3 (10.5%) | 2 (9.5%)  | 0.36    |
| TIMI 1–2 flow          | 11 (61.1%) | 14 (73.7%) | 0.32    |

Mean ± SD.

BMS, bare metal stent; MSG, microengineered stent grooves; TIMI, thrombolysis in myocardial infarction score.
expected cell frequency was <5 in any of the cells of the contingency table, otherwise the p-values were derived from Pearson’s $\chi^2$ test. Two-sided 95% CIs for proportions were calculated using exact methods. All statistical analyses were performed using SAS software (SAS Institute 9.4, Cary, NC).

**RESULTS**

**Demographic and procedural characteristics**

A total of 40 patients were randomized to each stent group and 37 patients (MSG n=19, BMS n=18) were included in the final analysis (3 patients were excluded due to poor OCT imaging quality). Both stent groups were properly matched for their baseline clinical and angiographic characteristics (table 1). Mean age and percentage of male gender were similar between the BMS and MSG groups (respectively: 69.43±9.95 vs 67.93±9.16, p=0.62; 72.2% vs 47.4%, p=0.11). The percentage of diabetic patients was also comparable between both groups and it was similar to previously published DES trials (BMS=29.4% vs MSG=26.3%, p=0.55). There was no difference in terms of the angiographic characteristics of the lesions treated; mainly target vessel diameter and lesion length. A summary of the most relevant clinical and procedural characteristics is presented in table 1.

**Stent-level neointimal proliferation and distribution analysis**

A summary of the OCT quantitative analysis is presented in table 2. The mean stent length measured by OCT was almost identical in the MSG and BMS groups. The patient (stent)-level analysis demonstrated ~12% reduction in neointimal thickness (NT) and smaller variations in the MSG compared with the BMS group (means 0.07 (0.06 to 0.08) vs 0.08 (0.05 to 0.145), p=0.83) (figure 3). This
reduction in neointimal proliferation in the MSG group was consistent in other variables including neointimal hyperplasia (NIH) area (14% reduction) and volume (19% reduction). Also, 61% of all BMS control stents had a mean NT <120 μm compared with 74% of the stents in the MSG group. These results were maintained in a more detailed analysis of NT distribution when the stent was divided in tertiles (proximal, mid and distal). In this analysis, a higher percentage of struts having <120 μm was consistently seen in the MSG group regardless of stent location (respectively: distal; 61% vs 64%; middle: 61% vs 71%; proximal: 68% vs 74%) (figure 4). Representative images of the typical OCT appearance at 3 weeks in both stent groups are shown in figure 5.

Strut-level analysis: coverage, proliferation and maturity analysis
A total of 7959 struts were analysed (~27 frames × ~200 struts per stent). At 3 weeks, virtually all struts analysed had evidence of tissue coverage by OCT (98.31% in BMS vs 97.17% in MSG). Partial strut coverage was observed in 2.8% (IQR 0.3–7.5%) of the MSG group and 1.7% (IQR 0.4–4.6%) of the BMS group (table 2). Covered protruding struts were observed in 18.7%...
(IQR 12.25–34.9%) of the MSG group and 17.4% (IQR 3.5–41.7%) of the BMS group. Fully covered embedded struts were observed in 74.2% in the MSG group (IQR 58.9–86.4%) and in 81.2 (IQR 49.8–95.5%) of the BMS group. Strut-level analysis demonstrated also reduction (~22%) in NT in the MSG compared with BMS group (median: 0.07 mm (0.04–0.15) vs 0.09 mm (0.04–0.17), p=0.83). In this analysis, most of the struts analysed (MSG=70% vs BMS=64%) had a mean NT <120 μm. The neointimal maturity analysis revealed that the percentage of homogenous neointima was comparable between groups (MSG=72.2% vs BMS=76.5%). However, while in the MSG group 27.8% of the struts analysed showed a heterogeneous neointima, in the BMS group there was a combination of heterogeneous (17.6%) and layered (5.9%) neointima (figure 6).

**Clinical follow-up**

During the 6 month clinical follow-up, no deaths were reported. One patient (5.3%) in the MSG group and two patients (11.1%) in the BMS group presented a MACE. There was a clinically driven target lesion revascularisation case in each group and additional clinically driven TVR case in the BMS group. There was a case of target-lesion-related MI reported in the MSG group (table 3). There was no case of stent thrombosis at 6 months in any of the groups.

**DISCUSSION**

DES continue to evolve towards the development of thinner metallic scaffolds and the use of more biocompatible polymers as drug carriers.16 Despite their undeniable clinical success, stent thrombosis and restenosis continue to occur overtime.17 Several studies suggest that both delayed healing and neoatherosclerosis

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**Table 3** Six-month clinical outcomes

|                                | BMS (n=18) | MSG (n=19) | p value |
|--------------------------------|------------|------------|---------|
| Death (total)                  | 0 (0%)     | 0 (0%)     | 1.00    |
| Hierarchical MACE at 6 months  | 2 (11.1%)  | 1 (5.3%)   | 0.52    |
| Clinically driven TLR          | 1 (5.6%)   | 1 (5.3%)   | 0.74    |
| Clinically driven TVR          | 1 (5.6%)   | 0 (0%)     | 0.49    |
| Target lesion-related MI       | 0 (0%)     | 1 (5.3%)   | 0.32    |
| Stent thrombosis               | 0 (0%)     | 0 (0%)     | 1.00    |

BMS, bare metal stent; MACE, major adverse cardiac event; MI, myocardial infarction; MSG, microengineered stent grooves; TLR, target lesion revascularisation; TVR, target vessel revascularisation.
are the most important biological mechanisms responsible for late stent failures. Experimental data suggest that the early phases of strut healing determine the long-term healing response of DES in humans. Clinical in vivo imaging studies have also shown that following stent implantation, an early proliferative response leads to accelerated neointimal formation and restenosis. Conversely, experimental studies suggest that accelerated strut endothelialisation results in the faster development of a thinner and more organised neointimal response. Then, in the evolving DES, the induction of rapid endothelialisation could potentially decrease not only the dependency of antiproliferative agents but also improve the safety profile of current generation DES.

In this study, we present the first experience using the MSG technology in humans. Over the last decade, the development of the MSG technology has sought to accelerate stent surface endothelialisation by creating specific parallel microgrooves (figure 1) using highly precise photolithographic techniques. Over the years, technological improvements have increased the manufacturing accuracy of the groove patterns progressing from micron to submicron resolutions. Improvements in edge, shape and depth definition of the microgrooves resulted in measurable increases in EC responses, demonstrating a peculiar sensitivity of the EC to defined groove features. In vitro studies have shown that MSG surfaces increase EC migration (by 2–3 times), maturity and functionality. These biological effects are independent of the material used (metals or polymers) and it is maintained in the presence of antiproliferative drugs. In addition, porcine studies demonstrated that MSG increased stent endothelialisation (by 17% at 3 days) and decreased NT (by 30% at 28 days) compared with identical BMS controls. In this study, we compared the patterns of stent healing of identical BMS exposing two different luminal surfaces (MSG vs flat) among patients undergoing PCI by performing OCT 3 weeks following stent implantation. To the best of our knowledge, our study represents one of the few studies presenting very early healing data following stent implantation. A striking finding in this study was the fact that in the absence of antiproliferative drugs strut coverage was in a very advanced stage of development by 3 weeks in both stent groups. This important biological finding highlights the significant advances stent technologies have had in the last decade. In the strut coverage analysis, BMS controls displayed a higher percentage of struts fully embedded in neointimal tissue. Although this finding may appear counterintuitive, such differences reflect the ability of the MSG surface to induce a thinner and more organised neointimal formation on the surface of the stent. In our analysis, the MSG group showed lower levels of neointimal formation at the strut and stent-level analysis. Interestingly, at this stage of healing the biological effect of the grooves appears to follow coronary flow favouring the proximal and medial parts of the stent. Furthermore, while in the BMS group layered neointimal tissue was seen in 6% of the OCT frames analysed, this OCT marker of delayed healing (fibrin deposits) was not seen in any of the OCT frames in the MSG group.

The most consistent biological finding seen in the MSG group was the reduction in neointimal proliferation. When measured as percentage of NIH tissue area relative to the total cross-sectional area of the stented segment, the percentage NIH area was lower through the length of the MSG group compared with BMS. Also, NIH volume measurements in cross-sectional imaging along the longitudinal axis of the MSG stent indicated lower volume of tissue coverage throughout most of the stent length compared with BMS (respectively: 8.9 (5.7–13.6) vs 11.0 (3.9–21.5), p=0.86). Furthermore, on strut-level analysis we observed similar level (~22%) of NT reduction in the MSG stent group (respectively: 0.09 (0.04–0.17) vs 0.07 (0.04–0.15), p=0.83) as seen in the previously published porcine studies (20% reduction). One of the most important findings is that in the MSG group most of the struts displayed an NT <120 μm throughout the length of the stent (figure 7). This finding is important as it shows the homogeneity of neointimal distribution throughout the surface of the stent.

Study limitations
This exploratory study using BMS without presence of anitproliferative drug was designed aiming to evaluate the impact of the MSG technology on stent healing. The sample size calculation was based on the estimated 20% reduction in neointimal proliferation induced by the MSG stent in the porcine studies; however, the study was

Figure 7 Average neointimal tissue thickness by decile from the most distal segment 1 to the most proximal 10 across the stent in each patient. BMS, bare metal stent; MSG, microengineered stent grooves.
underpowered to demonstrate statistical significances between the studied groups. Additionally, although OCT is a widely accepted tool for the evaluation of stent healing, their limited resolution does not allow the evaluation of true stent endothelialisation. Also, the classification used in this study to score and evaluate strut coverage using OCT aims to describe specific morphological patterns and may have little correlation with biological processes occurring in vivo. Then, the clinical implications of these findings are unknown. Finally, stent failure is a complex and multifactorial phenomenon occurring as the result of multiple inter-relayed factors evolving over time. This study provides only a snapshot at a single point in time and the final effects on stent healing need to be studied at long term in a larger population.

CONCLUSION
This clinical study presents the first-in-human implantation of the MSG technology in patients with ischaemic heart disease due to de novo coronary artery lesions. Early 3 weeks OCT analysis suggests that the MSG stents have the potential to induce lower levels of neointimal formation and more mature neointima compared with flat stent surfaces. Large imaging-based-randomised studies ideally in the presence of antiproliferative drugs are needed to confirm this hypothesis. Additionally, we observed higher level of OCT-derived neointimal maturity which indicates faster healing of the stent surface. In the strut coverage analysis, BMS controls displayed a higher percentage of struts fully embedded in neointimal tissue. Although this finding may appear counterintuitive, such differences reflect the ability of the MSG surface to induce a thinner and more organised neointimal formation on the surface of the stent. The biological effects of the MSG stent on EC migration are not affected by the presence of antiproliferative drugs, then this technology has the potential to improve the safety of devices in the presence of drug elution (ie, bioresorbable scaffolds). Further studies of this novel stent technology will assess the clinical outcomes at long-term follow-up.

REFERENCES
1. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18 334 patients. JACC Cardiovasc Interv 2013;6:1267–74.
2. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
3. Sprague EA, Tio F, Ahmed SH, et al. Impact of parallel micro-engineered stent grooves on endothelial cell migration, proliferation, and function: an in vivo correlation study of the healing response in the coronary swine model. Circ Cardiovasc Interv 2012;5:499–507.
4. Qi P, Chen S, Liu T, et al. New strategies for developing cardiovascular stent surfaces with novel functions (Review). Biointerphases 2014;9:022901.
5. de Mel A, Cousins BG, Seifalian AM. Surface modification of biomaterials: a quest for blood compatibility. Int J Biomater 2012;2012:70763.
6. Palmaz JC, Benson A, Sprague EA. Influence of surface topography on endothelialization of intravascular metallic material. J Vasc Interv Radiol 1999;10:439–44.
7. Bailey SR, Fuss C, Palmaz JC, et al. Surface micro grooves (MG) improve endothelialization rate in vitro and in vivo. J Am Coll Cardiol 2001;37:704.
8. Sprague EA, Luo J, Palmaz JC. Human aortic endothelial cell migration onto stent surfaces under static and flow conditions. J Vasc Interv Radiol 1997;8:93–92.
9. Palmaz JC, Bailey S, Marton D, et al. Influence of stent design and material composition on procedure outcome. J Vasc Surg 2002;36:1031–9.
10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
11. Varno V, Kiviniemi TO, Nammas W, et al. Early vascular healing after titanium-nitride-oxide-coated stent versus platinum-chromium everolimus-eluting stent implantation in patients with acute coronary syndrome. Int J Cardiovasc Imaging 2016;32:1031–9.
12. La Manna A, Prati F, Capodanno D, et al. Head-to-head comparison of early vessel healing by optical coherence tomography after implantation of different stents in the same patient. J Cardiovasc Med 2011;12:328–33.
13. Nishinari M, Shimohama T, Tojo T, et al. Two-week interval optical coherence tomography: imaging evidence on neo-intimal coverage completion after implantation of the Endeavor zotarolimus-eluting stent. Catheter Cardiovasc Interv 2013;82:E871–E878.
14. Annaia AP, Lehtinen T, Kiviniemi TO, et al. Vascular healing early after titanium-nitride-oxide-coated stent implantation assessed by optical coherence tomography. J Invasive Cardiol 2013;25:188–9.
15. Gonzalo N, Serruys PW, Okamura T, et al. Optical coherence tomography patterns of stent restenosis. Am Heart J 2009;158:284–93.
16. Nelson A, Costa JR, New drug-eluting stents: an overview on biodegradable and polymer-free next-generation stent systems. Circ Cardiovasc Interv 2010;3:384–93.
17. Keng SH, Park KW, Kang DY, et al. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. Eur Heart J 2014;35:1147–58.
18. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
19. Inoue T, Croce K, Morooka T, et al. Vascular inflammation and repair: implications for re-endothelialization, restenosis, and stent thrombosis. JACC Cardiovasc Interv 2011;4:1057–66.
20. Prati F, Romagnoli E, Valgimigli M, et al. Randomized comparison between 3-month Cre8 DES vs. 1-month Vision/ Multilink8 BMS neointimal coverage assessed by OCT evaluation: the DEMONSTRATE study. Int J Cardiol 2014;176:904–9.
21. Lee JM, Choe W, Kim BK, et al. Comparison of endothelialization and neointimal formation with stents coated with antibodies against CD34 and vascular endothelial-cadherin. Biomaterials 2012;33:8917–27.
22. Bartorelli AL, Trabattoni D, Fabbrocchi F, et al. Synergy of passive coating and targeted drug delivery: the tacrolimus-eluting Janus CarboStent. J Interv Cardiol 2003;16:499–505.