Evaluation of safety and efficacy of biodegradable polymer-based sirolimus-eluting stent in a porcine coronary artery model

Gaku Nakazawa1,**, Tooru Nakamura-Hirotã2,*

1Department of Cardiology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
2ShinSei Lab Co., Ltd, 83-6 Hiramori, Okubo, Uji, Kyoto 611-0033, Japan

Received: 1 July 2018 / Accepted: 24 October 2018
© Japanese Society of Biorheology 2018

Abstract Aims: The safety and efficacy of biodegradable polymer-based drug-eluting stents remain unclear. The aim of this study was to evaluate the safety and efficacy of biodegradable polymer-based sirolimus-eluting stent (SES) in a porcine coronary model. Methods and Results: Sirolimus and biodegradable PLGA (50:50) polymer were used to coat a diamond-like carbon-coated bare metal stent (MOMO-BMS). The sirolimus content was 100 μg/cm² (SES100) or 140 μg/cm² (SES140). Stents were implanted in porcine coronaries. The animals were euthanized at 1 and 3 months (n = 4 each). At 1 month, histological analysis revealed that both SES100 and SES140 had significantly higher fibrin scores than MOMO-BMS, and like MOMO-BMS, they decreased to baseline level at 3 months. Furthermore, both SES100 and SES140 showed less neointima than MOMO-BMS at 1 month (0.72 ± 0.35, 0.75 ± 0.20, 1.05 ± 0.42, respectively; p = 0.34), and this was maintained at 3 months with no increase of inflammatory reaction. Conclusion: The results indicate that the novel biodegradable polymer-based SES is safe and effective.

Keywords biodegradable polymer, sirolimus, drug-eluting stent, diamond-like carbon, porcine coronary model

Introduction

Since the advent of first generation drug-eluting stents (DES), the occurrence of in-stent restenosis, which is the major limitation of intracoronary stent therapy, has been reduced with controlled drug release from durable polymers [1, 2]. However, late thrombotic events have been noted with the use of DES, and have emerged as a concern [3–5]. Pathologic studies have reported various causes of late stent thrombosis in different phases after placement, such as delayed arterial healing, hypersensitivity reaction, excessive fibrin deposition with malapposition, and neoatherosclerosis [6–9]. One possible device-related complications is hypersensitivity reaction which is believed to occur due to poor biocompatibility of the polymer [10].

In order to both improve the mechanical properties and to provide biocompatibility, a metallic stent may be coated with various materials such as carbon [11, 12], silicon carbide [13] or tantalum [14]. Among these materials, a diamond-like carbon (DLC) stent coating has been introduced as a new stent design with improved biocompatibility. The coating reduces contact with biomaterials, and decreases metal ion release and thrombogenicity [15–18]. A thinner strut, for example, reduces intimal hyperplasia and thrombotic potential, improving clinical outcomes [19, 20]. In the first-human study of DLC-coated bare metal stent (MOMO-BMS) with thin 70 μm strut Kesavan S et al demonstrated proof of concept for the safety and feasibility of using MOMO-BMS in patients with single focal de novo lesions presenting with stable and unstable coronary artery disease [21]. In addition, Ando et al, also reported a prospective multi-center registry to evaluate efficacy and safety of the newly developed MOMO-BMS system [22].

The porcine coronary model has been used to evaluate the efficacy and safety of DES, and appears to resemble the reaction to intracoronary devices in humans if the time points are properly chosen [23, 24]. Previously, we reported a progressively increasing inflammatory reaction over time with placement of SES in the porcine coronary model [23], resembling reactions found in human autopsies [8], (if the humans involved were still living, you would just say “found in humans”) although the incidence of this phenomenon is considered to be much lower in humans. Therefore, using the porcine coronary artery model for a 3–6 month
period is suitable method for examining long term biocompatibility [24] in humans. Furthermore, we have demonstrated that biodegradable polymer-based sirolimus A9-eluting stent was safer than durable polymer-based sirolimus-eluting stent (SES) in a porcine coronary Model [25]. However, the vascular response to biodegradable polymer-based SES with DLC is unclear.

The aim of this study was to evaluate the safety and efficacy of biodegradable polymer-based SES in a porcine coronary model.

Materials and Methods

**Preparation of biodegradable polymer-based sirolimus eluting stents**

Diamond-like carbon (DLC)-coated bare metal stents (MOMO-BMS: 3.0 × 18 mm or 3.5 × 18 mm) were supplied by Japan Stent Technology Co., Ltd. The stent is a cobalt-chromium stent platform and has thin 70 μm strut. The drug eluting stents consists of biodegradable poly(lactide-co-glycolic acid) (PLGA(50:50), LACTEL Absorbable Polymers, USA) polymer-coated sirolimus-eluting stents with the cumulative drug release profile of Cypher stent (50% drug release at 8 days, 80% drug release at 28 days and 100% drug release at 90 days) and the MOMO-BMS platform. The conformal coating consists of a base-coating layer (containing sirolimus and PLGA polymer) and top-coating layer (containing PLGA only). The sirolimus contents of the base-coating layers were 100 μg/cm² (SES100) and 140 μg/cm² (SES140), respectively. The top-coating layer contains 260 μg/cm² of PLGA polymer to achieve the same cumulative drug release profile of Cypher stent.

**SEM imaging of coating surface and HPLC analysis of sirolimus contents in SES**

Scanning electron microscope (SEM) imaging was performed on a Keyence SEM (VHX-D500). Images were acquired ranging from 100x to 500x magnification. The amount of sirolimus content in the coated layer of SES was analyzed by high pressure liquid chromatography (HPLC) (Prominence HPLC system, Shimadzu, Japan) with a J’sphere ODS-H80 column (4.6 × 75 mm, YMC Co., Japan), the elution being monitored at 278 nm. The elution method is a gradient of acetonitrile from 5% (W/W) to 100%. We purchased sirolimus from Selleck Chemicals (USA) and used it as a reference standard. The cumulative sirolimus release of SES in 20 mM phosphate buffered saline at 37 degrees Celsius was detected by measuring the absorbance at 278 nm.

**Animal preparation and procedures**

Eight mini-swine were used in the present study. Diamond-like carbon (DLC)-coated bare metal stents (MOMO-BMS: 3.0 × 18 mm or 3.5 × 18 mm, Japan Stent Technology Co., Ltd, Okayama) and biodegradable PLGA polymer-based sirolimus-eluting stents (SES) containing two differential sirolimus contents (100 μg/cm² and 140 μg/cm²) were employed, with one of each type implanted into each pig (one stent per one vessel). Stent implantation was performed at Surpass Inc (USA). Animals were euthanized at 1 and 3 months (n = 4 each). Following euthanasia, implanted stents were gained from the pig coronary arteries at CVPath institute (USA). These stents were subjected to histologic examination to analyze vascular responses in Tokai University.

All animals were premedicated with oral clopidogrel (75 mg/day) and aspirin (81 mg/day) beginning 2 days before the procedure, and these medications were continued until the day of euthanasia. After anesthesia with isoflurane, surgical access was obtained via a femoral artery using general sterile techniques. During cardiac catheterization, heparin (10,000 IU) was injected to maintain an activated clotting time (ACT) of 250–300 seconds. Vessel allocation to experimental groups was predetermined to distribute the different stent types equally in three different coronary arteries. Stent deployment was performed using a 1:1.2 stent-to-artery diameter ratio.

At 1 and 3 months, the animals were euthanized under general anesthesia, by IV injection of pentobarbital euthanasia solution (100 mg/kg) and/or potassium (40 mEq). The hearts were excised and pressure perfused with 0.9% saline until cleared of blood, followed by pressure perfusion fixation in 10% neutral buffered formalin until hardening of the heart muscle was clearly perceptible.

**Histologic preparation and assessments**

To assess the safety and efficacy of implanted stents, we measured neointimal thickness and analyzed inflammation score, fibrin score and injury score as shown in the following formulas and Table 1. The stented arteries were embedded in methylmethacrylate resin. After polymerization, sections were taken from every 2 mm of the stent (for a total of 4–5 sections) and stained with hematoxylin and eosin and Movat’s Pentachrome. Histomorphometric analysis was performed for quantifying neointimal growth and assessment of arterial injury and inflammation.

Vessel injury scores were calculated according to the Schwartz method [26]. The vessel injury scores were shown in Table1. The cross sectional areas (external elastic lamina [EEL], internal elastic lamina [IEL], lumen area, and neointimal thickness) of each section were measured with digital morphometry (WinROOF Image processing Software, Ver.6, Mitani Corp., Tokyo, Japan). Neointimal thickness is measured as the distance from the inner surface of each stent strut to the luminal border. Area measurements are used to calculate vessel layer areas with the following formulas:
Medial Area = EEL Area – IEL Area

Neointimal Area = IEL Area – Lumen Area

% Stenosis = \[1 – (\text{Lumen Area} / \text{IEL Area})\]

Ordinal data were collected for each stent section on fibrin deposition, granulomatous reactions, and the presence of giant cells around the stent struts. Each was expressed as a percentage of the total number of struts in each section. The overall neointimal inflammation and fibrin value was scored for each section as previously described [27]. Table 1 also shows the neointimal inflammation scores and fibrin scores, respectively.

Statistical analysis

Values were expressed as mean ± standard deviation. One way analysis of variance ANOVA was used to compare statistical differences in continuous values between the groups. Nonparametric score data, including injury, fibrin, and neointimal and adventitial inflammation were compared using a Wilcoxon Kruskal-Wallis test. A value of \( p < 0.05 \) was considered statistically significant (JMP software, Cary, NC).

Results

SEM imaging of coating surface and HPLC analysis of sirolimus contents in SES

Fig. 1 shows an image of DLC-coated stent platform (MOMO-BMS) and a SEM image of the coating of a biodegradable polymer-based sirolimus-eluting stent (SES). The conformal coating of drug and polymer are layered onto the MOMO-BMS stent platform. The sirolimus content in the coating layer of the SES was analyzed by reverse-phase HPLC. The resulting HPLC profile is shown in Fig. 2. The cumulative sirolimus release of SES in 20 mM phosphate buffered saline at 37 degrees Celsius was measured at 278 nm. The resulting drug release profile is shown in Fig. 3.

Stent implantation

Stent implantation was performed successfully in 8 pigs (3 vessels per pig) with no differences in quantitative coronary analysis (QCA) data including in stent minimum lumen diameter and stent length. All pigs survived the study period without illness.

Histologic observations

One month group

MOMO-BMS and SES showed patent lumens with no thrombus formation at 1 month. A total of 4 sections for BMS and 8 sections for SES100 (containing 100 μg/cm² sirolimus) and SES140 (containing 140 μg/cm² sirolimus)

| Table 1 Overall scoring attribute | Score | Description of assigned weight |
|-----------------------------------|-------|--------------------------------|
| **Injury Score** (Using the method described by Schwartz et al) | 0 | Internal elastic lamina (IEL) intact, endothelium typically denuded, media may be compressed but not lacerated |
| | 1 | IEL lacerated, media typically compressed but not lacerated |
| | 2 | IEL lacerated, media visibly lacerated, external elastic lamina (EEL) intact but may be compressed |
| | 3 | EEL lacerated, typically large lacerations of media extending through EEL, coil wires sometimes residing in adventitia |
| **Neointimal Inflammation Score** | 0 | <25% struts with fewer than 10 inflammatory cells |
| | 1 | Up to 25% struts with greater than 10 inflammatory cells |
| | 2 | 25-50% struts with greater than 10 inflammatory cells |
| | 3 | >50% struts with greater than 10 inflammatory cells |
| | 4 | 2 or more struts with associated granulomatous inflammatory reactions |
| **Fibrin Score** | 0 | No fibrin is appreciated (or only small strands) |
| | 1 | At least 25% of struts involving confluent fibrin that surrounds up to 25% of the strut circumference |
| | 2 | At least 50% of struts involving confluent fibrin that surrounds >25% of strut circumference |
| | 3 | ALL struts with confluent fibrin surrounding >50% of strut circumference OR 25–50% of struts with confluent fibrin involving >25% of strut circumference with extension or bridging between struts |
were analyzed. Mild neointimal formation was observed in SES, whereas MOMO-BMS showed a relatively large amount of neointimal formation. However, a higher fibrin score was obtained in SES100 and SES140 compared to MOMO-BMS (Table 2: 1.42 ± 0.50, 1.17 ± 0.58, 0.08 ± 0.17, respectively; p = 0.005). There were no significant differences between MOMO-BMS and SES in various parameters including inflammatory reaction and neointimal formation (Table 2, Fig.4).

Three month group

MOMO-BMS and SES showed patent lumens with no thrombus formation at 3 months. A total of 4 sections for each BMS and 8 sections for SES100 and SES140 were analyzed. Decreased inflammatory reactions were observed in all groups and the fibrin score of SES decreased to a basal level similar to that of MOMO-BMS. As in the 3 month results, there were no significant histologic differences between MOMO-BMS and SES. A minimal inflammatory reaction was seen in both groups (Table 3, Fig.5).

Discussion

The major findings of the current study were 1) a novel biodegradable polymer-based SES effectively suppress neointimal formation; 2) consistent minimal inflammatory reaction and fibrin accumulation with the biodegradable polymer-based SES compared to BMS.

Histologic examination revealed a decrease in both fibrin accumulation and inflammatory reaction in the SES group (SES100 and SES140) and the MOMO-BMS group during the three month period of implantation. There was signifi-
cant difference in fibrin accumulation at 1 month between
the SES group and the MOMO-BMS group (P < 0.01). The
higher fibrin score in SES indicates that sirolimus effec-
tively functions as a suppressor of neointimal formation in
coronary artery. Furthermore, SES showed minimal neo-
timal area at both 1 and 3 months, whereas MOMO-BMS

| Table 2 | Histologic assessments at 1 month (n = 4) |
|---------|------------------------------------------|
|         | MOMO-BMS | SES100 | SES140 | p value |
| EEL [mm²] | 7.55 ± 0.89 | 8.19 ± 1.45 | 7.89 ± 1.53 | 0.80 |
| Stent Area [mm²] | 6.06 ± 0.87 | 6.66 ± 1.00 | 6.40 ± 1.07 | 0.70 |
| Lumen [mm²] | 5.01 ± 1.11 | 5.93 ± 0.94 | 5.66 ± 1.21 | 0.50 |
| Neointima [mm²] | 1.05 ± 0.42 | 0.72 ± 0.35 | 0.75 ± 0.20 | 0.34 |
| %Stenosis | 18.0 ± 8.9 | 10.9 ± 4.5 | 12.3 ± 5.2 | 0.31 |
| Inflammation Score | 0.21 ± 0.25 | 0.25 ± 0.32 | 0.42 ± 0.50 | 0.71 |
| Fibrin Score | 0.08 ± 0.17 | 1.42 ± 0.50 | 1.17 ± 0.58 | 0.005 |
| Injury Score | 0.12 ± 0.10 | 0.19 ± 0.03 | 0.16 ± 0.10 | 0.53 |

Fig. 4 Representative histologic images at 1 month
Mild neointimal formation (yellow arrows) was observed in all SES (B–C), whereas MOMO-BMS showed a relatively large amount of neointimal formation (A). A large amount of fibrin accumulation (red arrows) was observed in all SES compared with the MOMO-BMS.

| Table 3 | Histologic assessments at 3 months (n = 4) |
|---------|------------------------------------------|
|         | MOMO-BMS | SES100 | SES140 | p value |
| EEL [mm²] | 8.36 ± 1.60 | 7.56 ± 0.33 | 8.28 ± 1.56 | 0.65 |
| Stent Area [mm²] | 7.00 ± 1.32 | 6.38 ± 0.23 | 6.95 ± 1.29 | 0.68 |
| Lumen [mm²] | 5.94 ± 1.17 | 5.60 ± 0.36 | 6.21 ± 1.54 | 0.75 |
| Neointima [mm²] | 1.06 ± 0.33 | 0.78 ± 0.22 | 0.74 ± 0.35 | 0.33 |
| %Stenosis | 15.2 ± 4.7 | 12.4 ± 3.8 | 11.3 ± 5.9 | 0.53 |
| Inflammation Score | 0.08 ± 0.17 | 0.17 ± 0.19 | 0.08 ± 0.17 | 0.75 |
| Fibrin Score | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.17 ± 0.33 | 0.41 |
| Injury Score | 0.15 ± 0.09 | 0.21 ± 0.11 | 0.20 ± 0.12 | 0.73 |
displayed a larger amount of neointimal area during this study period. However, there was no significant difference in inflammatory reaction and injury score between the SES group and the MOMO-BMS group. These results confirm the safety of biodegradable polymer-based sirolimus-eluting stent with the same profile of cumulative drug release of Cypher stent, which is consistent with our previous preclinical study and clinical study findings [21, 25]. Together, these findings suggest that our animal study model was able to demonstrate long term biocompatibility.

As described above, although the porcine coronary model used in the present study is considered suitable for biocompatibility testing, animal models are not perfect. The major limitation of device testing in preclinical studies is that the turnover and proliferation in animals is much faster than in humans, and although drug release kinetics in DES do not vary between species, the possibility of differing responses between animals and humans does exist. In the present study, extending the study period to 1 year may be appropriate, since the completion of PLGA(50:50) polymer degradation in SES may take 6–9 months (Although in vitro complete degradation of LACTEL PLGA(50:50) polymer takes 1–3 months). However, we believe that the 3 month period was sufficient to evaluate long term biocompatibility and safety because, the first-in-human study of MOMO-BMS demonstrated proof of concept for the safety and feasibility of the MOMO-BMS in patients with single focal de novo lesions presenting with stable and unstable coronary artery disease [21]. Furthermore, prospective multi-center registry to evaluate efficacy and safety of the newly developed diamond-like carbon-coated cobalt-chromium coronary stent system (MOMO-BMS) [28]. Our results suggest that a further study is needed to make safe and efficacious newer generation SES.

There are limitations to the current study. We have used a limited number of animals and stents (n = 4 each) per time-point. Therefore, some results, such as the histologic assessment, did not reach statistical significance. However, this is a preclinical study using juvenile miniswine. The variability between individual pigs receiving stents is not as high as that of humans who may have differing extent and duration of coronary artery disease and more variable reactions.

**Conclusion**

A novel biodegradable polymer based SES with DLC were associated with minimal inflammation during the three month period of implantation.

**Acknowledgements** This study is in-part supported by Okayama Prefecture Industrial Promotion Foundation of Japan.

**References**

1. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002; 346: 1773–80.
2. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O’Shaughnessy C, Caputo RP, Kereikas DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003; 349: 1315–23.

3. McFadden EP, Stabile E, Egar R, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. Lancet. 2004; 364: 1519–21.

4. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, Mueller C, Jeger R, Bader F, Osswald S, Kaiser C. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: An observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006; 48: 2584–91.

5. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: A cause for concern. Circulation. 2007; 115: 1440–55.

6. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: Delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006; 48: 193–202.

7. Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: An autopsy study. Circulation. 2008; 118: 1138–45.

8. Palmerini T, Biondi-Zoccai G, Riva DD, Mariani A, Savini C, Di Eusorio M, Geneux P, Frati G, Marullo AG, Landoni G, Greco T, Branzi A, De Servi S, Di Credico G, Taglieri N, Williams MR, Stone GW. Risk of stroke with percutaneous coronary intervention compared with on-pump and off-pump coronary artery bypass graft surgery: Evidence from a comprehensive network meta-analysis. Am Heart J. 2013; 165: 910–70.

9. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, Ladich E, Kolodgie FD, Finn AV, Virmani R. The pathology of neointimal hyperplasia in human coronary restenosis compared to de novo lesions. J Am Coll Cardiol. 2011; 57: 1314–22.

10. Virmani R, Guagliumi G, Farb A, Musumeci G, Greico N, Motta T, Mihalskis L, Tespili M, Valsecchi O, Kolodgie FD. Localized neointimal hyperplasia and coronary late thrombosis secondary to a sirolimus-eluting stent: Should we be cautious? Circulation. 2004; 109: 701–5.

11. Kim HJ, Moon MW, Lee KR, Seok HK, Han SH, Ryu JW, et al. The Mechanical stability of a diamond-like carbon coated nitinol vascular stent under cyclic loading. Thin Solid Films. 2008; 517: 1146–50.

12. Airoldi F, Colombo A, Tavano D, Stankovic G, Klugmann S, Paolillo V, et al. Comparison of diamond-like carbon-coated stents versus uncoated stainless steel stents in coronary artery disease. Am J Cardiol. 2004; 93: 474–7.

13. Unverdorben M, Sattler K, Degenhardt R, Fries R, Abt B, Wagner E. Comparison of a silicon carbide coated stent versus a non-coated stent in humans: the Tenax-versus Nir-Stent Study (TENISS). J Interv Cardiol. 2003; 16: 325–33.

14. Silva RA, Walls M, Rondot B, Da Cunha Belo M, Guidoin R. Electrochemical and microstructural studies of tantalum and its oxide films for biomedical applications in endovascular surgery. J Mater Sci Mater Med. 2002; 13: 495–500.

15. Schaefer O, Lohrmann C, Winterer J, Kotter E, Langer M. Endovascular treatment of superficial femoral artery occlusive disease with stents coated with diamond-like carbon. Clin Radiol. 2004; 59: 1128–31.

16. Gutensohn K, Beythien C, Bau J, Fenner T, Grew P, Koester R, et al. In vitro analyses of diamond-like carbon coated stents: reduction of metal ion release, platelet activation, and thrombogenicity. Thromb Res. 2000; 99: 577–85.

17. Antonucci D, Bartorelli A, Valenti R, Montorsi P, Santoro GM, Fabbrocchi F, et al. Clinical and angiographic outcome after coronary arterial stenting with the cabostent. Am J Cardiol. 2000; 85: 821–5.

18. Bartorelli AL, Trabattoni D, Montorsi P, Fabbrocchi F, Galli S, Ravagnani P, et al. Aspirin alone antiplatelet regimen after intracoronary placement of the CarboStent: the ANTARES study. Cathet Cardiovasc Interven. 2002; 55: 150–6.

19. Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schuhlen H, Neumann FJ, Fleckenstein M, Pfaffertt C, Seyfarth M, Schonig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO) trial. Circulation. 2001; 103: 2816–21.

20. Pache J, Kastrati A, Mehilli J, Schuhlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sambolberger U, Schmidt C, Muller M, Dirschinger J, Schonig A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STERO-2) trial. J Am Coll Cardiol. 2003; 41(8): 1283–8.

21. Kesavan S, Strange JW, Johnson TW, Flohr-Roese S, Baumbach A. First-in-man evaluation of the MOMO cobalt-chromium coronary-coated stent. EuroIntervention. 2013; 8(9): 1012–8.

22. Ando K, Ishii K, Tada E, Kato A, Hiejima H, Aoto K, Kobayashi K, Tsutui H, Nakahama M, Nakashima H, Uchikawa S, Kanda J, Yasuda S, Yajima J, Kitaibayashi H, Sakurai S, Nakashiki K, Inoue N, Noike H, Hasebe T, Sato T, Yamasaki M, Kimura T. Prospective multi-center registry to evaluate efficacy and safety of the newly developed diamond-like carbon coated-chromium coronary stent system. Cardiovasc Interv Ther. 2017; 32(3): 225–32.

23. Nakazawa G, Finn AV, Ladich E, Ribichini F, Coleman L, Kolodgie FD, Virmani R. Drug-eluting stent safety: Findings from preclinical studies. Expert Rev Cardiovasc Ther. 2008; 6: 1379–91.

24. Virmani R, Kolodgie FD, Farb A, Lafont A. Drug eluting stents: Are human and animal studies comparable? Heart. 2003; 89: 133–8.

25. Nakazawa G, Shinke T, Iijichi T, Matsumoto D, Otake H, Torii S, Hiranuma N, Ohsue T, Otsuka F, Shite J, Hirata K, Ikari Y. Comparison of vascular response between durable and biodegradable polymer-based drug eluting stents in a porcine coronary artery model. EuroIntervention. 2014; 10(6): 717–23.

26. Schwartz RS, Huber KC, Murphy JG, Edwards WD, Camrud AR, Vliestra RE, Holmes DR. Restenosis and the proportional neointimal response to coronary artery injury: Results in a porcine model. J Am Coll Cardiol. 1992; 18: 267–74.

27. Granada JF, Inamasu S, Abboodi MS, Tellez A, Milewski K, Wallace-Bradley D, Parker S, Rowland S, Nakazawa G, Vorpahl M, Kolodgie FD, Kuluza GL, Leon MB, Virmani R. Development of a novel prohealing stent designed to deliver sirolimus from a bioabsorbable abluminal matrix. Circ Cardiovasc Interv. 2010; 3(5): 257–66.

28. Ando K, Ishii K, Tada E, Kataoka K, Hiihata A, Goto K, Kobayashi K, Tsutui H, Nakahama M, Nakashima H, Uchikawa S, Kanda J, Yasuda S, Yajima J, Kitaibayashi H, Sakurai S, Nakashiki K, Inoue N, Noike H, Hasebe T, Sato T, Yamasaki M, Kimura T. Prospective multi-center registry to evaluate efficacy and safety of the newly developed diamond-like carbon coated-chromium coronary stent system. Cardiovasc Interv Ther. 2017; 32(3): 225–32.