VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2023, Vol. 30, No. 6, 881–891
DOI: 10.5603/CJ.a2023.0006

ISSN 1897–5593
eISSN 1898–018X

A novel polymer-free everolimus-eluting stent with a nitrogen-doped titanium dioxide film inhibits restenosis and thrombosis in a swine coronary model

Dae Young Hyun[1], Xiongyi Han[2], Dae Sung Park[2], Munki Kim[2], Jun Kyu Park[3], Kyung Hoon Cho[1], Doo Sun Sim[1, 4], Young Joon Hong[1, 4], Youngkeun Ahn[1, 4], Myung Ho Jeong[1, 4]

[1]Department of Cardiology, Chonnam National University Hospital, Gwangju, Republic of Korea
[2]Cardiovascular Research Center, Chonnam National University Hospital, Gwangju, Republic of Korea
[3]Cell & Growth Factor Biotechnology, Ltd., Seoul, Republic of Korea
[4]Department of Cardiology, Chonnam National University Medical School, Hwasun, Republic of Korea

Abstract

Background: *Short-term outcomes regarding the safety and efficacy of a polymer-free everolimus-eluting stent (EES) with a nitrogen-doped titanium dioxide (N-TiO_2) film in a swine coronary model have been reported. However, the long-term results of the use of this type of stent have not yet been evaluated or compared to those of other polymer-free coronary stents. Therefore, this study aimed to determine the mid- to long-term safety and efficacy of a polymer-free EES with an N-TiO2 film in a swine coronary model.*

Methods: *Polymer-free EES with N-TiO2 films (n = 30) and polymer-free sirolimus-eluting stents (SES; n = 30) were implanted in 30 pigs. Quantitative coronary analysis and optical coherence tomography were conducted immediately and at 1 (quantitative coronary analysis only), 3, and 6 months after stenting. Histopathologic examinations were performed at 1, 3, and 6 months after stenting.*

Results: *The polymer-free EES group had a lower percentage of neointimal growth than the polymer-free SES group at 3 months (22.5% ± 11.4% vs. 32.1% ± 12.3%; p < 0.001). The polymer-free EES group had a lower fibrin score than the polymer-free SES group at 1 month (1.9 ± 0.45 vs. 2.5 ± 0.54; p = 0.001). The re-endothelialization rates were similar between groups. The polymer-free EES group had a lower percentage of the area of stenosis than the polymer-free SES group throughout the follow-up period.*

Conclusions: *The novel polymer-free EES with an N-TiO_2 film has superior safety and efficacy than the polymer-free SES at the 6-month follow-up in a swine model.* (Cardiol J 2023; 30, 6: 881–891)

Key words: drug-eluting stent, optical coherence tomography, polymer, restenosis, titanium dioxide

Address for correspondence: Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI, FAPSIC, Principal Investigator of the Korea Acute Myocardial Infarction Registry, Director of The Heart Research Center of Chonnam National University Hospital Designated by the Korea Ministry of Health and Welfare, 42, Jebong-ro, Dong-gu, Gwangju 61469, Republic of Korea, tel: +82.62-220-6243, fax: +82.62-228-7174, e-mail: myungho@chollian.net

Received: 22.10.2021 Accepted: 17.01.2023 Early publication date: 30.01.2023

Introduction

Although bare metal stent (BMS) implantation has a lower restenosis rate than that of balloon angioplasty, the reduction of the restenosis rate by BMS is limited [1]. The use of durable polymer drug-eluting stents (DP-DES) has significantly decreased restenosis rates [2, 3]. However, DP-DES may induce stent thrombosis through local hypersensitivity reactions and inflammation caused by polymer persistence [4, 5]. To overcome this limitation, new-generation DES, including biodegradable polymer DES (BP-DES) and polymer-free DES, have been developed [6, 7].

This study evaluated the safety and efficacy of a novel polymer-free everolimus-eluting stent (EES) with a nitrogen-doped titanium dioxide (N-TiO_2) film, comparing them with those of a commercial polymer-free sirolimus-eluting stent (SES). To the best of our knowledge, this is the first pre-clinical study comparing a polymer-free EES with an N-TiO_2 film with another polymer-free stent design in a swine model with up to 6 months of follow-up.

Methods

The novel polymer-free EES with an N-TiO_2 film was designed by Chonnam National University Hospital (Gwangju, Republic of Korea) and manufactured by Cell & Growth Factor Biotechnology (CG Bio Co., Ltd., Seoul, Republic of Korea). The stent strut based on cobalt-chromium was coated with N-TiO_2 using a plasma-enhanced chemical vapor deposition process (Fig. 1) [8, 9]. The stent was covered with everolimus using an electrospinning technique [10]. This stent has been patented in the United States (patent numbers 09795987 and 10343184) and was approved for clinical trials by the Ministry of Food and Drug Safety in June 2020.

Characterization of the stent surface

Roughness of the stent surface

The surface roughness of the BMS, BMS coated with N-TiO_2, polymer-free EES coated with N-TiO_2, and polymer-free SES was assessed using atomic force microscopy (NX10; Park System, Suwon, Republic of Korea). Ra (arithmetic mean roughness), a commonly used roughness parameter, is measured using the average of the absolute values of height deviations from the mean line within the evaluation length. The higher the Ra value, the greater the difference between the peaks and valleys of the stent surface. The scan size was 10–20 μm.

Hydrophobicity of the stent surface

The contact angle test is a tool to evaluate the wettability of a surface. Hydrophobicity, defined as a contact angle over 90°, intensifies with larger contact angles. The degree of the dispersion of 2 μL of water on the stent surface was evaluated using a contact angle analyzer (Phoenix 300; SEO, Suwon, Republic of Korea). The hydrophobicity test was performed 10 times for each stent.

Study groups

A total of 30 pigs were assigned to 1 month (n = 10), 3 months (n = 10), and 6 months of follow-up (n = 10) from March to December 2018. One polymer-free EES with an N-TiO_2 film (3.0 × 16 mm; CG Bio Co., Seoul, Republic of Korea) and polymer-free SES (Coroflex ISAR® 3.0 × 16 mm; B. Braun. Melsungen, Hessen, Germany) were randomly implanted into two different coronary arteries in 1 pig. Yorkshire × Landrace F1 crossbred neutered male pigs were followed up for 1 month (n = 10; 15-20 kg, 3 months of age, Chuwol grandparent farm in southwest Republic of Korea). Male minipigs (trade name micro-pig; T-type pig) were followed up for 3 months (n = 10) and 6 months (n = 10) (15–20 kg, 24 months of age, APURES in northwest Republic of Korea) (Fig. 2). Contrary to previous studies that used DP-DES for the control group, this study used the polymer-free SES [10, 11]. This study conformed to the Guide for the Care and Use of Laboratory Animals and was approved by the Chonnam National University Hospital Animal Ethics Committee based on the Animal Protection Act (Institutional Review Board approval number: CNU IACUC-H-2018-5).

Anesthesia for experimental animals

General anesthesia was induced using an intramuscular injection of 12 mg/kg of ketamine and 8 mg/kg of xylazine. Oxygen was supplied using an intubation tube, and saline was supplied through the ear veins. Then, local anesthesia with 2% lidocaine was sterilely induced at the center of the animal's neck. The left carotid artery of the pig was cut, and a 7-Fr sheath was inserted. A dose of 200 IU/kg of heparin was administered as a single injection into the artery before advancing the guiding catheter.

Experimental process

Before stenting, coronary angiography (CAG) was performed to identify the coronary artery segment for the 3.0 × 16 mm stent implantation. Quantitative coronary analyses (QCA) were

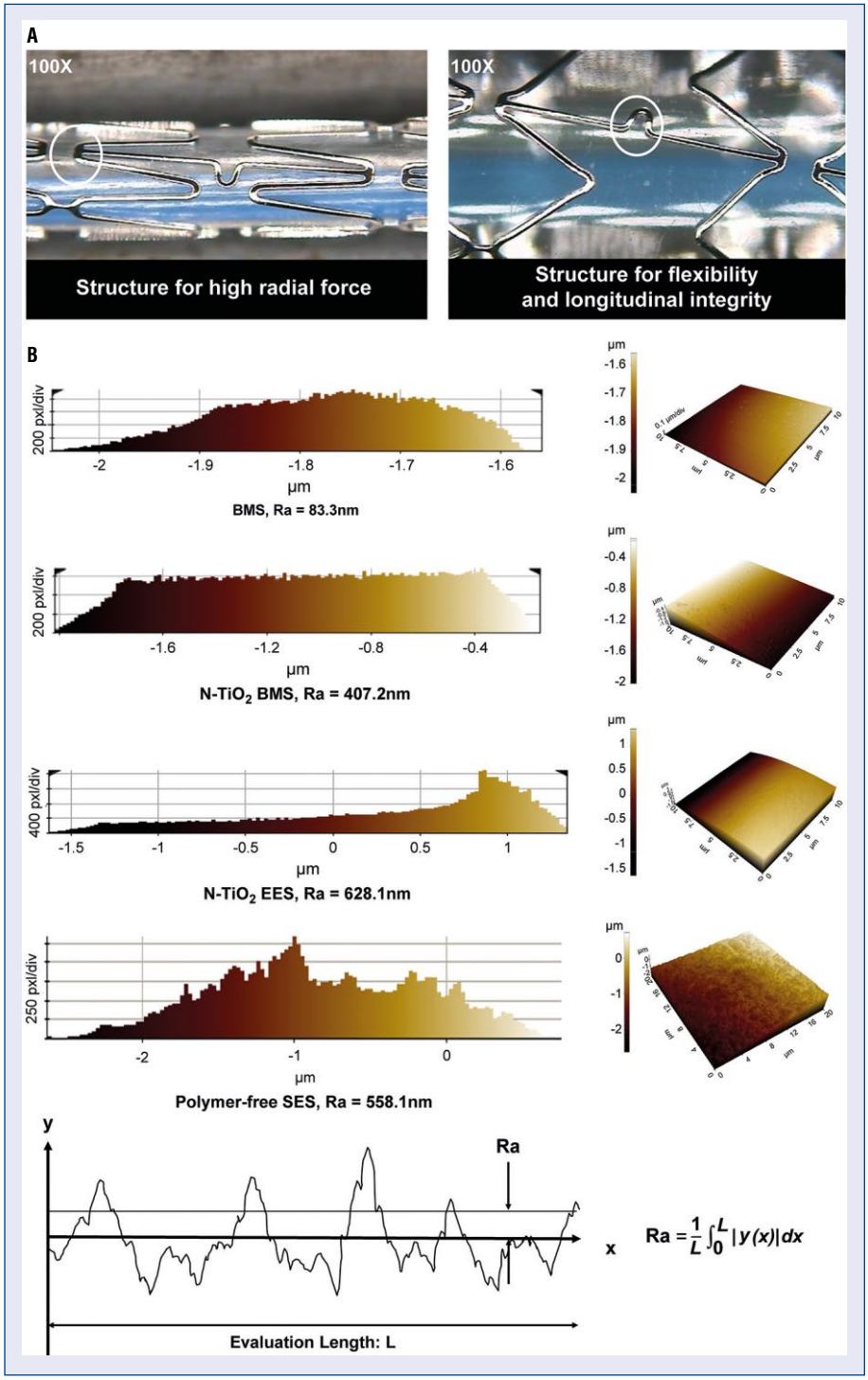

Figure 1. Evaluation of the stent surface; **A.** Microscopic findings of polymer-free everolimus-eluting stent (EES) with nitrogen-doped titanium dioxide (N-TiO_2) films; **B.** The stent surface roughness is measured using atomic force microscopy; BMS — bare metal stent; Ra — roughness average; SES — sirolimus-eluting stent.

performed to evaluate the coronary lumen diameter and length. Then, the balloon was expanded for 30 s. The stent-to-vessel ratio ranged from 1.1:1 to 1.3:1. Optical coherence tomography (OCT) was performed to ensure optimal stent expansion and apposition, together with the absence of edge dissections. After stenting, the left carotid artery was ligated, and the skin of the neck was sutured.

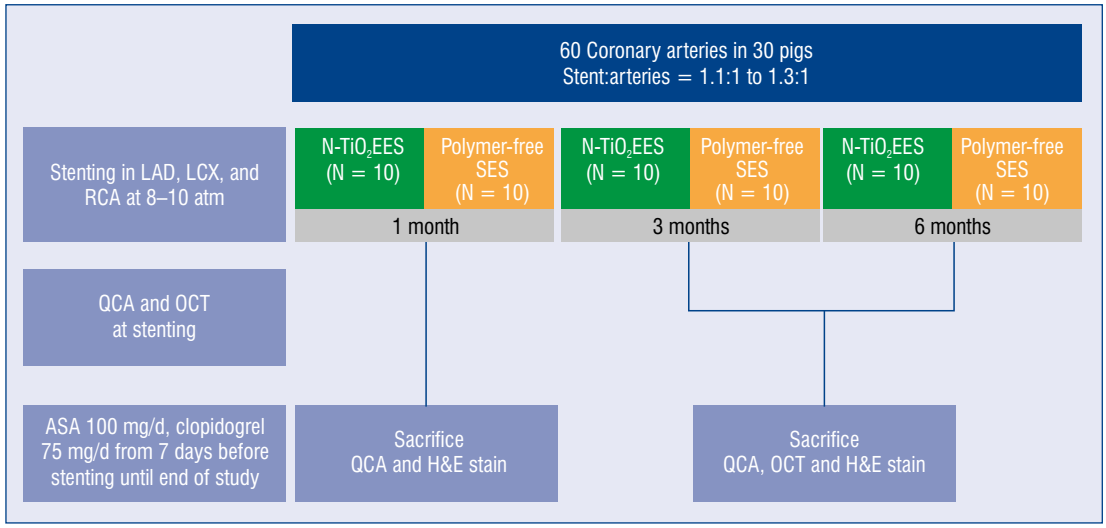

Figure 2. Study flowchart. Experimental and control stents were implanted in 30 pigs, and the stent placement was evaluated at 1, 3, and 6 months; ASA — acetylsalicylic acid; EES — everolimus-eluting stent; H&E — hematoxylin and eosin; LAD — left anterior descending artery; LCX — left circumflex artery; N-TiO_2 — nitrogen-doped titanium dioxide; OCT — optical coherence tomography; QCA — quantitative coronary analysis; RCA — right coronary artery; SES — sirolimus-eluting stent.

Acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) were administered 7 days before stenting and until the end of the study period. Because the healing response and neointimal growth pattern after stent implantation occur 5- to 6-times faster in pigs than in humans, 1-, 3-, and 6-month follow-up periods were used during this study to represent 1.5 to 3 years of follow-up for humans who receive DES [12]. The right carotid artery was used for performing CAG, QCA, and OCT during follow-up.

Histopathologic study

The experimental animals fasted the day before anesthesia. After follow-up CAG, 40 mL of potassium chloride was injected through a catheter sheath to induce euthanasia. The heart was removed through an incision in the left thoracic cavity. Perfusion fixation with 4% formalin was performed for more than 24 h at a perfusion pressure of 70 mmHg. The stented coronary artery was isolated, and three sections were prepared to estimate the coronary artery lesion. Samples were embedded in paraffin. To evaluate re-endothelialization of the stent, an immunohistochemical analysis was performed. The tissue samples were divided into 5-μm-thick sections using a rotary microtome. To reduce autofluorescence, 0.1% Sudan black B was used for 20 min. To prevent non-specific reactivity, 3% fetal bovine serum in phosphate-buffered saline was used for 60 min. An anti-mouse monoclonal cluster of differentiation 31 (CD31) antibody (1:100; Abcam, Cambridge, Massachusetts, USA) was used for immunohistochemistry. Streptavidin Alexa Fluor® 488-conjugated anti-mouse IgG (1:400; Invitrogen) was used as the secondary antibody for fluorescence microscopy.

Analysis

QCA evaluation

Two experienced examiners conducted the QCA. CAG was performed after the administration of nitroglycerin into the coronary artery. The analysis was conducted using a QCA system (CAAS QCA Workstation; Pie Medical Imaging, Maastricht, Netherlands). The reference vessel diameter, stenosis diameter in the target lesion, and minimal lumen diameter were measured. Late lumen loss (LLL) was defined as the difference between the minimal lumen diameter immediately after stent implantation and at the time of follow-up.

OCT evaluation

Optical coherence tomography with C7-XRTM (Light Imaging Inc., Westford, Massachusetts, USA) was used to observe the strut apposition during the stent implantation and the neointimal response in the coronary vessels during follow-up. A DragonflyTM OPTIS catheter (Abbott Vascular, Chicago, IL, USA) was used for the acquisition. The optical catheter was previously purged with contrast (Omnihexol 350; Korea United Pharm Inc., Seoul, Republic of Korea). A 6-Fr guiding catheter

was used, and the guidewire was inserted into the coronary artery where the stent was located. The OCT probe was advanced along the guidewire and placed at the intended scanning location using C-arm guidance. A total of 30 mL of contrast was injected into the coronary artery at a pressure of 300 psi/s using an automatic injector, thus enabling OCT image acquisition using the non-occlusive technique. A 54-mm coronary segment was imaged at a pullback speed of 20 mm/s and a rotation speed of 100 frames/s.

Histopathologic evaluation

Experts at Chonnam National University Hospital and CG Bio Inc. conducted the histopathologic analysis. The external and internal elastic laminae, lumen, stent, and neointimal areas and stent strut thickness were measured. Damage to the vessel walls caused by stent overexpansion was assessed by the following scoring system: disruption of the internal elastic lamina, 1 point; disruption of the media, 2 points; and disruption of the external elastic lamina, 3 points. The inflammatory index was used to quantify the degree of inflammatory cell infiltration into the entire vessel. When the inflammatory cells were scattered, the inflammatory index score was 1. When they were concentrated around one-half of the struts, the score was 2. When they were concentrated around all struts, the score was 3. Fibrin deposition was scored from 0 to 3 and assessed for each stent section. The rate of re-endothelialization was calculated based on the percentage of the lumen area covered by endothelial cells.

Statistical analysis

All measurements are expressed as mean ± standard deviation. They were analyzed using unpaired t-test and one-way analysis of variance. Statistical analyses were conducted using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Results

Stent surface roughness and hydrophobicity

The average surface roughness was 83.3 nm for the BMS and 407.2 nm after the plasma-enhanced chemical vapor deposition of N-TiO_2. The surface of the EES with an N-TiO_2 coating was rougher than that of the polymer-free SES (628.1 nm vs. 558.1 nm) (Fig. 1). The water contact angles were 124.3° ± 0.18° for the BMS, 117.0° ± ± 0.06° for the BMS with an N-TiO_2 coating, 108.1° ± 0.18° for the EES with an N-TiO_2 coating, and 123.8° ± 0.11° for the polymer-free SES. The hydrophobicity values of the stent surfaces were significantly different between the BMS and the BMS with an N-TiO_2 coating ($p < 0.001$), between the BMS with an N-TiO_2 coating and the EES with an N-TiO_2 coating ($p < 0.001$), and between the EES with an N-TiO_2 coating and the polymer-free SES ($p < 0.001$) (Fig. 3).

Coronary lumen diameters and LLL

The baseline coronary lumen diameters were not significantly different between the follow-up groups. Stent implantation was successful in all animals, with a thrombolysis in myocardial infarction flow grade of 3. After stent implantation, the coronary lumen diameters were not significantly different between the follow-up groups. On all follow-up QCA, the coronary lumen diameter ($p = 0.732$ at 1 month, $p = 0.186$ at 3 months, $p = 0.314$ at 6 months) and LLL ($p = 0.520$ at 1 month, $p = 0.218$ at 3 months, $p = 0.449$ at 6 months) were not different in the comparison groups (Table 1). No death occurred during the follow-up period.

Neointimal area and volume

The percentage of neointimal area obstruction in the polymer-free SES was larger than that in the polymer-free EES with an N-TiO_2 film at 3 months (32.1% ± 12.3% vs. 22.5% ± 11.4%, $p < 0.001$) but was not significant at 6 months of follow-up (28.8% ± 13.4% vs. 27.9% ± 10.5%, $p = 0.524$). No significant differences in the neointimal volume between the two stent groups at 3 and 6 months of follow-up were recorded (Fig. 4, Table 1).

Histopathologic outcomes

No significant differences in the injury and inflammatory scores between the two stent groups at 1 month were observed. The fibrin score with the polymer-free SES was significantly higher than that with the polymer-free EES with an N-TiO_2 film ($p = 0.001$). The area of stenosis with the polymer-free SES was larger than that with the polymer-free EES with an N-TiO_2 film ($p = 0.003$). The injury, inflammatory, and fibrin scores were not significantly different between the two stent groups at 3 months. The area of stenosis with the polymer-free SES was larger than that with the polymer-free EES with an N-TiO2 film ($p = 0.019$). At 6 months, the injury, inflammatory, and fibrin scores were not significantly different between the two stent groups. The area of stenosis

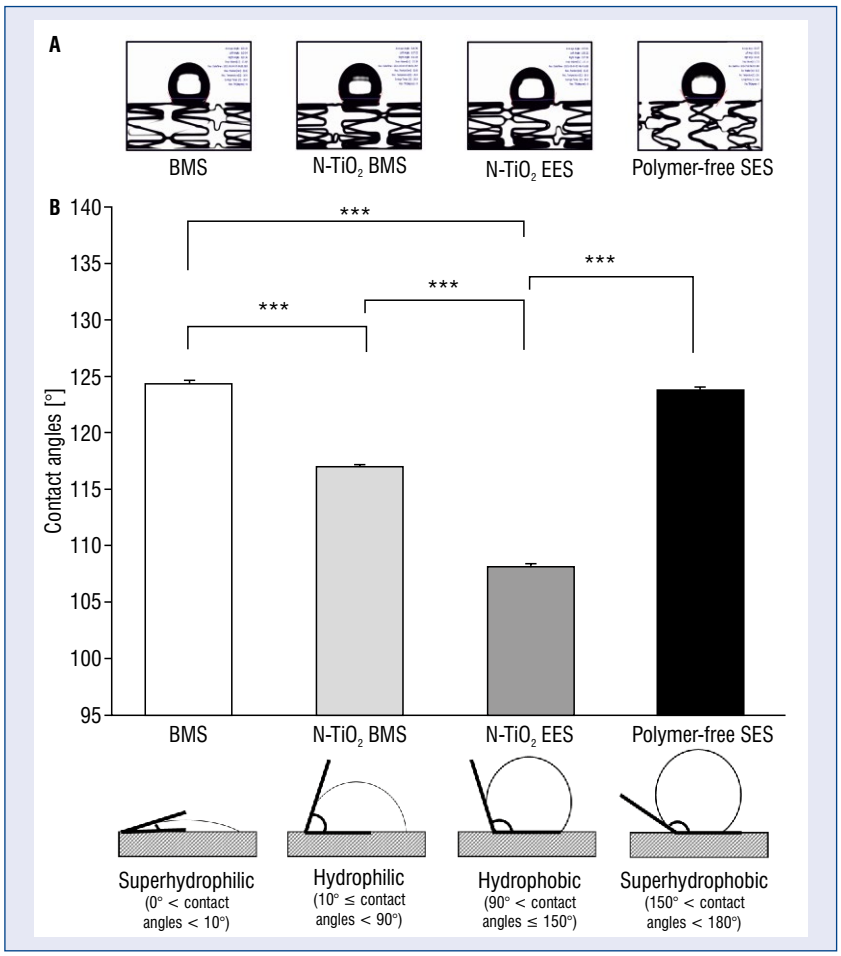

Figure 3. Stent surface hydrophobicity; **A.** Surface contact angles of the stents; **B.** Surface contact angles are compared between two stents using a contact angle analyzer; ***p < 0.001; BMS — bare metal stent; EES — everolimus-eluting stent; N-TiO_2 — nitrogen-doped titanium dioxide; SES — sirolimus-eluting stent.

with the polymer-free SES was larger than that with the polymer-free EES with an N-TiO_2 film (p = 0.002) (Figs. 4, 5, Table 1). The rates of re-endothelialization were not significantly different between the two stent groups at 1, 3, or 6 months (Fig. 6, Table 1).

Discussion

The main findings of this study can be summarized as follows: A polymer-free EES with an N-TiO_2 film showed borderline superior efficacy than that of a polymer-free SES for up to 6 months in a swine study, as indicated by the smaller neointimal area obstruction on OCT at 3 months and the smaller stenosis area on QCA at 6 months of follow-up. Although the polymer-free EES with an N-TiO_2 film resulted in a lower fibrin score than that of the polymer-free SES at 1 month, all other parameters of inflammation, re-endothelialization, and safety were not significantly different.

The use of DP-DES decreased the rate of in-stent restenosis from 15–30% to less than 15% after 12 months [5]. However, DP-DES have a high probability of developing very late stent thrombosis. The remaining stent material, including the polymer, induced chronic inflammation and a hypersensitivity reaction, which may cause very late stent thrombosis. Although the polymer-free DES was developed to improve these problems, it has not shown meaningful outcomes compared with those of the DP-DES. In the Intracoronary Stenting and Angiographic Results: Test Efficacy of Three Limus-Eluting Stents (ISAR-TEST) 2 and ISAR-TEST 5 trials, polymer-free DES had similar death, myocardial infarction, and revascularization rates (including definite or probable stent thrombosis) compared to those of DP-DES [13–15].

Table 1. Coronary artery morphometric measurements.

	N-TiO_2 EES (n = 30)	Polymer-free SES (n = 30)	P
1 month	**n = 10**	**n = 10**	
QCA:			
Before stenting			
Vessel diameter [mm]	2.73 ± 0.24	2.73 ± 0.24	0.984
After stenting			
Lumen diameter [mm]	2.89 ± 0.23	2.80 ± 0.25	0.446
Stent-to-artery ratio	1.06 ± 0.03	1.03 ± 0.07	0.232
Follow-up			
Lumen diameter [mm]	2.49 ± 0.32	2.43 ± 0.40	0.732
Late lumen loss [mm]	0.38 ± 0.31	0.47 ± 0.21	0.520
Histologic findings:			
Injury score	1.01 ± 0.02	1.00 ± 0.02	0.637
Inflammatory score	1.00 ± 0.00	1.02 ± 0.07	0.118
Fibrin score	1.89 ± 0.45	2.53 ± 0.54	0.001
Stenosis area [%]	30.5 ± 6.7	35.5 ± 10.4	0.003
Re-endothelialization rate [%]	78.4 ± 14.7	66.2 ± 27.0	0.193
3 months	**n = 10**	**n = 10**	
QCA:			
Before stenting			
Vessel diameter [mm]	2.77 ± 0.24	2.80 ± 0.26	0.738
After stenting			
Lumen diameter [mm]	2.95 ± 0.25	3.00 ± 0.22	0.625
Stent-to-artery ratio	1.07 ± 0.03	1.08 ± 0.05	0.613
Follow-up			
Lumen diameter [mm]	2.50 ± 0.32	2.32 ± 0.28	0.186
Late lumen loss [mm]	0.50 ± 0.37	0.73 ± 0.36	0.218
OCT:			
Neointimal area [%]	22.5 ± 11.4	32.1 ± 12.3	< 0.001
Neointimal volume [%]	22.9 ± 11.6	29.6 ± 11.2	0.205
Histologic findings:			
Injury score	1.06 ± 0.10	1.05 ± 0.10	0.472
Inflammatory score	1.04 ± 0.07	1.05 ± 0.09	0.871
Fibrin score	0.22 ± 0.46	0.18 ± 0.43	0.620
Stenosis area [%]	34.4 ± 10.2	39.7 ± 14.0	0.019
Re-endothelialization rate [%]	81.3 ± 19.8	78.8 ± 20.6	0.732
6 months	**n = 10**	**n = 10**	
QCA:			
Before stenting			
Vessel diameter [mm]	2.59 ± 0.20	2.69 ± 0.25	0.368
After stenting			
Lumen diameter [mm]	2.93 ± 0.19	2.90 ± 0.15	0.719
Stent-to-artery ratio	1.13 ± 0.08	1.08 ± 0.06	0.119
Follow-up			
Lumen diameter [mm]	2.58 ± 0.28	2.41 ± 0.40	0.314
Late lumen loss [mm]	0.40 ± 0.28	0.53 ± 0.45	0.449
OCT:			
Neointimal area [%]	27.9 ± 10.5	28.8 ± 13.4	0.524
Neointimal volume [%]	27.6 ± 9.7	30.8 ± 12.9	0.531
Histologic findings:			
Injury score	1.07 ± 0.11	1.07 ± 0.14	0.797
Inflammatory score	1.04 ± 0.23	1.02 ± 0.05	0.413
Fibrin score	0.00 ± 0.00	0.02 ± 0.14	0.322
Stenosis area [%]	45.5 ± 7.5	51.7 ± 12.3	0.002
Re-endothelialization rate [%]	92.6 ± 11.2	85.8 ± 15.8	0.208

Data are presented as mean ± standard deviation; EES — everolimus-eluting stent; N-TiO_2 — nitrogen-doped titanium dioxide; OCT — optical coherence tomography; QCA — qualitative comparative analysis; SES — sirolimus-eluting stent

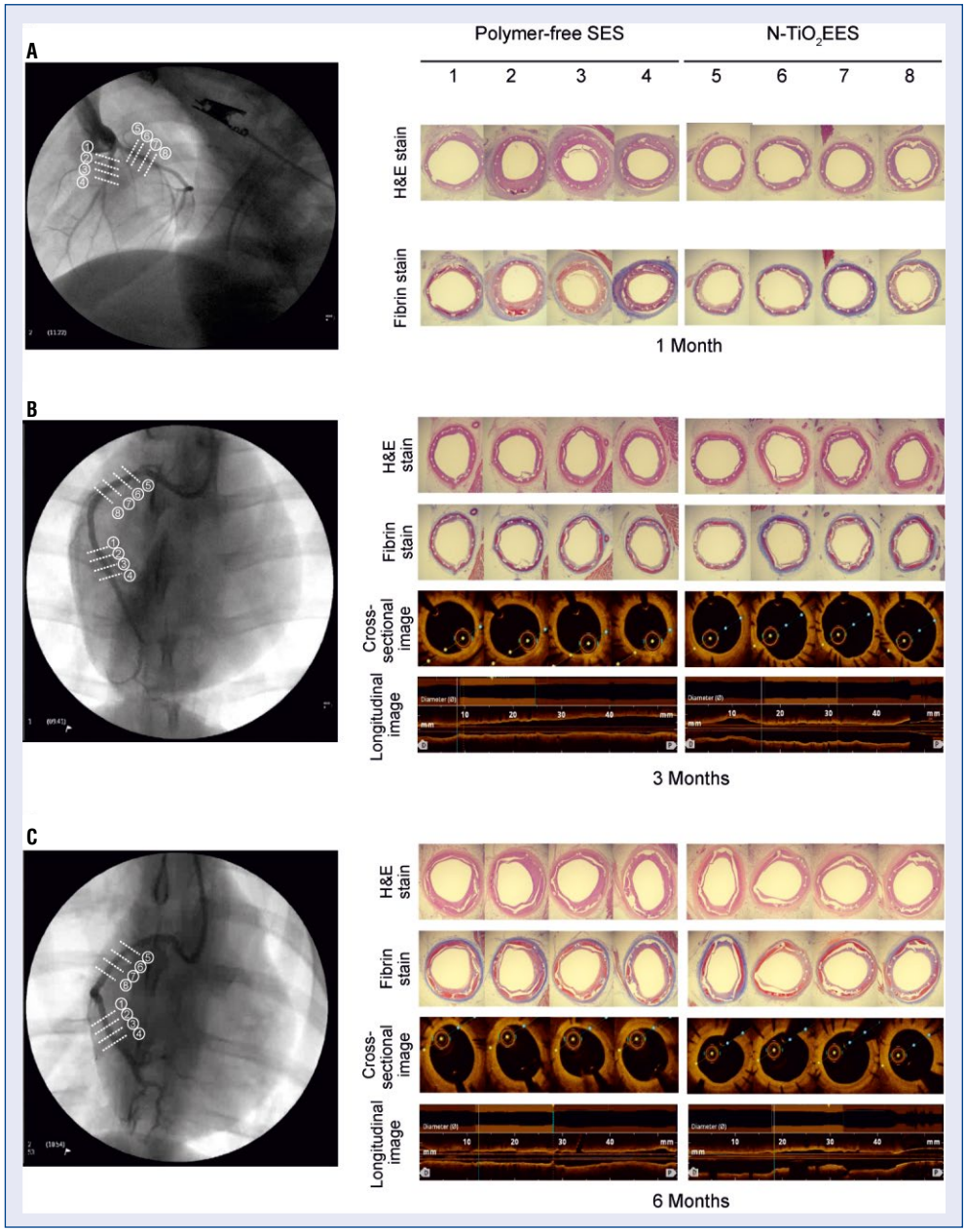

Figure 4. Histopathologic and optical coherence tomography findings at 1 (**A**), 3 (**B**), and 6 (**C**) months after stent implantation. Numbers above the histological section images indicate corresponding numbers on the coronary angiogram on the left panel; EES — everolimus-eluting stent; H&E — hematoxylin and eosin; N-TiO_2 — nitrogen-doped titanium dioxide; SES — sirolimus-eluting stent.

In contrast, fluoropolymer-coated stents demonstrated outstanding results in *in vitro* tests. Fluoropolymers bind tightly with albumin and passivate the surface to protect against thrombogenic materials [16]. The platelet adherence and inflammatory cell density were lower with the fluoropolymer-coated EES compared with the polymer-free biolimus A9-coated stent in *ex vivo* swine arteriovenous shunt model experiments [17]. To overcome the limitations of the previous polymer-free DES, the polymer-free EES with N-TiO_2 films used differentiated coating technologies and drugs.

Several technologies have been used to coat the polymer-free DES with drugs, including use of microporous surfaces, direct coating, crystallization of the drug, and inorganic porous coatings. These coating technologies affect the drug loading, drug-eluting rate, and platelet activation [18]. The stent platform of the polymer-free SES used in the control group was sandblasted to create

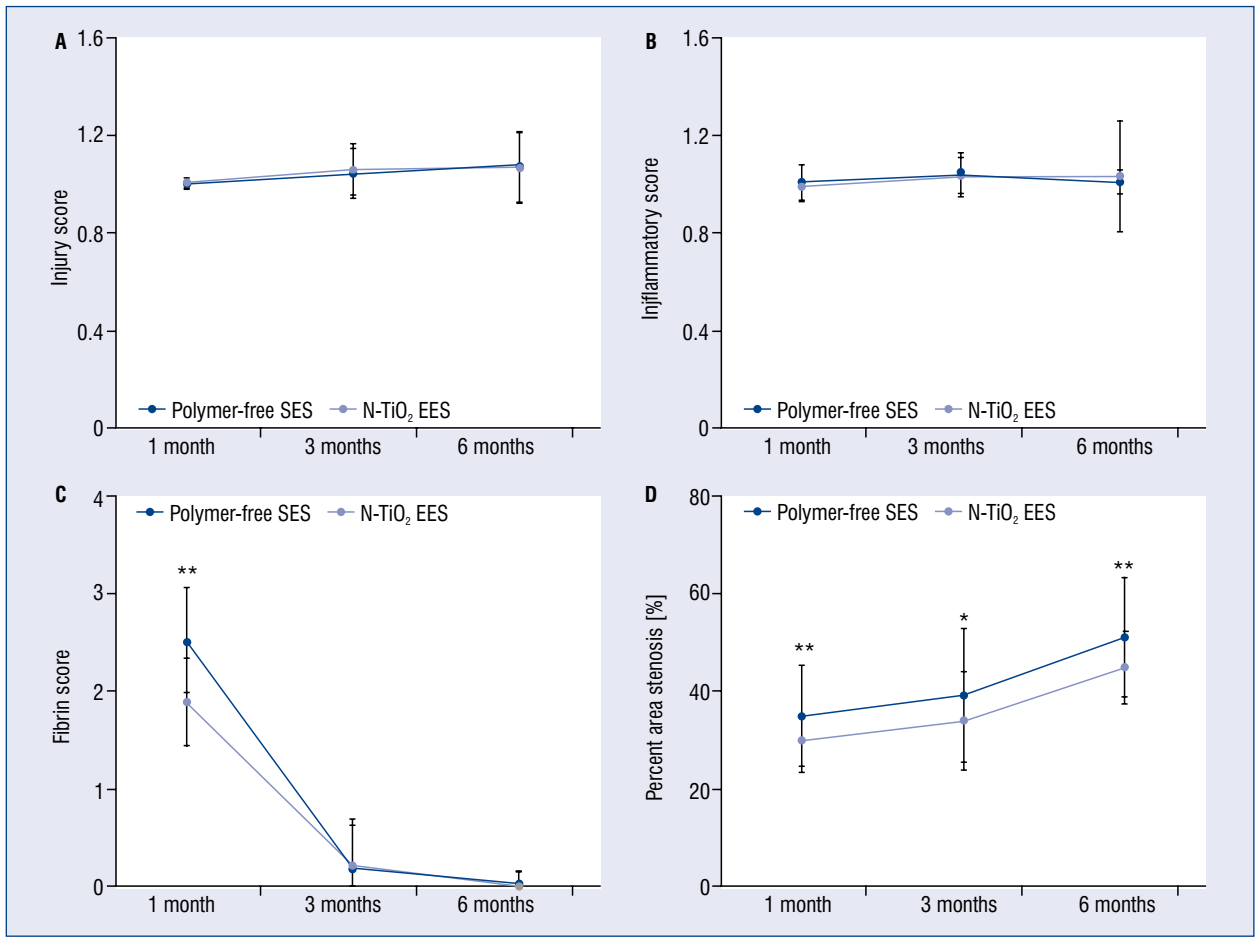

Figure 5. Histopathologic changes at 6 months after stent placement. Changes in the injury score (**A**), inflammatory score (**B**), fibrin score (**C**), and stenosis area (%) (**D**); *p < 0.05, **p < 0.01; EES — everolimus-eluting stent; N-TiO_2 — nitrogen-doped titanium dioxide; SES — sirolimus-eluting stent.

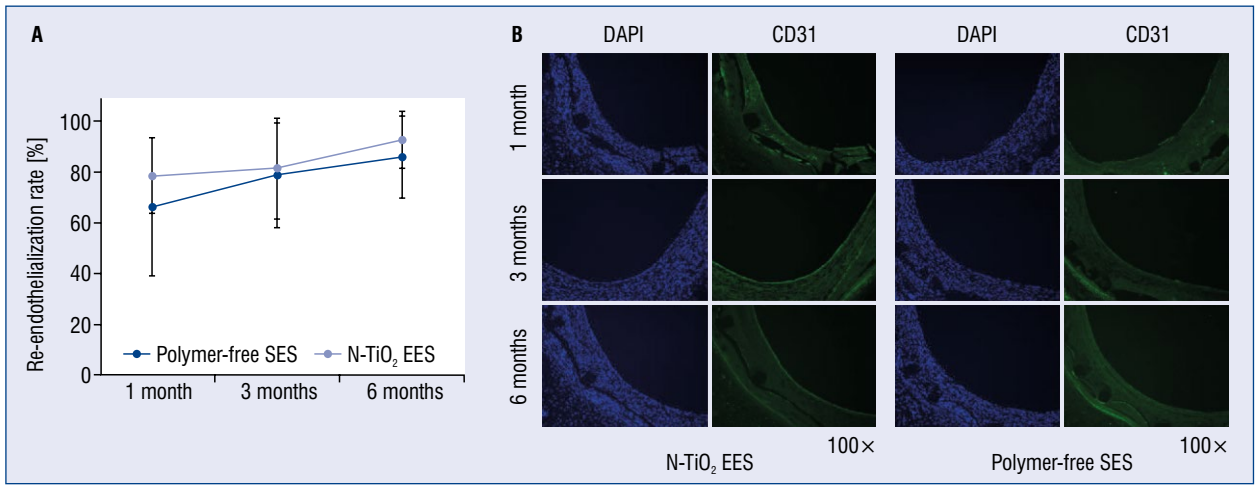

Figure 6. Re-endothelialization rates and immunohistochemical staining at 1, 3, and 6 months after stent placement; Re-endothelialization rate changes (**A**) and immunohistochemical staining at 1, 3, and 6 months after stent implantation (**B**); CD31 — cluster of differentiation 31; DAPI — 4,6-diamidino-2-phenylindole; EES — everolimus-eluting stent; N-TiO_2 — nitrogen-doped titanium dioxide; SES — sirolimus-eluting stent.

a microporous surface that allows drug deposition. The novel polymer-free EES used specific coating technologies, such as an inorganic porous coating with an N-TiO_2 film. A plasma-enhanced chemical vapor deposition process with N-TiO_2 creates a coarse surface on the stent for the drug. One study showed that the smooth surface of the stent had less thrombogenicity and induced less neointimal hyperplasia [19]. However, in the study by Dibra et al. [20], rough stent surfaces did not increase LLL and restenosis rates compared with those of smooth stent surfaces in patients with coronary artery disease who underwent percutaneous coronary intervention. Another study showed that microscopic parallel grooves improved the endothelialization compared with that of smooth surfaces [21]. The process of N-TiO_2 coating also results in an improved hydrophobicity at the stent surface (Fig. 3). The hydrophilic surface tends to improve the endothelial healing and reduce the platelet adhesion. The ultra-hydrophilic surface--treated BMS showed less intimal hyperplasia compared with that of the second-generation DES in a swine coronary model [22]. During inflammation, monocytes are more likely to adhere to hydrophobic surfaces than to hydrophilic surfaces [23].

Drugs (such as limus analogs and paclitaxel) may be used to reduce neointimal hyperplasia, which is related to restenosis, by suppressing the activation of smooth muscle and inflammatory cells. However, re-endothelization may also be inhibited, consequently increasing the stent thrombosis. Use of the EES resulted in less neointimal hyperplasia, less fibrin deposition, and more re-endothelialization compared with use of the SES in a rabbit model of iliac artery stenting [24]. Although similar clinical outcomes were reported for the EES, a zotarolimus-eluting stent, and SES in the BIO-RESORT trial [25], the EES had a lower risk of very late stent thrombosis and better outcomes than the SES in the Scandinavian Organization for Randomized Trials with Clinical Outcome IV trial [26]. Because of the influences of the coating technology and drugs used, the percentage of the area of stenosis during 6 months of follow-up and the fibrin score, which reflects the state of arterial healing, at 1 month after the stent placement were lower in the polymer-free EES with an N-TiO_2 film than in the polymer-free SES. Similar inflammatory scores and re-endothelialization rates between the two groups throughout the follow-up period can also be influenced by these factors.

The novel polymer-free EES with an N-TiO_2 film showed good biocompatibility and favorable 1-month outcomes in previous swine coronary models [10, 11]. In the preclinical study of Cho et al. [27], the polymer-free EES with an N-TiO_2 film also demonstrated similar 6-month OCT and histopathologic findings compared with those of fluoropolymer-coated stents. Although a significant difference was not observed between the two stent types, the polymer-free EES with an N-TiO_2 film had a fibrin score of 0 at 6 months (0 vs. 0.07 ± 0.11, $p = 0.180$). Therefore, reasonable mid- to long-term outcomes regarding restenosis and stent thrombosis are expected based on the results of our study. The polymer-free DES with an N-TiO_2 film can be an alternative to DP-DES and other polymer-free DES.

Limitations of the study

However, this study has some limitations. First, the stent was implanted in a healthy swine coronary artery that had no significant atherosclerosis. Second, the type of pigs used during the 1-month follow-up period was different from the type of pigs used during the other follow-up periods. Finally, the follow-up period was limited to 6 months. Further research is warranted to obtain data regarding the longer-term safety and efficacy.

Conclusions

The domestic polymer-free EES with an N-TiO_2 film outperformed the safety and efficacy of the polymer-free SES in experimental and pre-clinical 6-month follow-up tests in many aspects. The novel polymer-free EES with an N-TiO_2 film may be used effectively in clinical practice.

Acknowledgments

This study was supported by a grant from the Korea Health Technology R&D Project (HI13C1527), Ministry of Health and Welfare, Republic of Korea. It was also supported by funds from Chonnam National University Hospital Biomedical Research Institute (BCRI-21054) and the Ministry of Science and ICT; the Ministry of Trade, Industry, and Energy; the Ministry of Health and Welfare; and the Ministry of Food and Drug Safety (1711138916, KMDF_PR_20200901_0280), Republic of Korea. This article underwent English language editing by Editage.

Conflict of interest: The Chonnam National University Hospital is a patentee of the stent. Among the authors, Dae Sung Park, Jun Kyu Park, Doo Sun Sim, and Myung Ho Jeong are registered as inventors. The other authors have nothing to disclose.

References

1. Brophy JM, Belisle P, Joseph L, et al. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. Ann Intern Med. 2003; 138(10): 777–786, doi: 10.7326/0003-4819-138-10-200305200-00005, indexed in Pubmed: 12755549.
2. Bønaa KH, Mannsverk J, Wiseth R, et al. NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. N Engl J Med. 2016; 375(13): 1242–1252, doi: 10.1056/NEJMoa1607991, indexed in Pubmed: 27572953.
3. Moses JW, Leon MB, Popma JJ, et al. SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med. 2003; 349(14): 1315–1323, doi: 10.1056/NEJMoa035071, indexed in Pubmed: 14523139.
4. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? Circulation. 2004; 109(6): 701–705, doi: 10.1161/01.CIR.0000116202.41966.D4, indexed in Pubmed: 14744976.
5. Torrado J, Buckley L, Durán A, et al. Restenosis, stent thrombosis, and bleeding complications: navigating between Scylla and Charybdis. J Am Coll Cardiol. 2018; 71(15): 1676––1695, doi: 10.1016/j.jacc.2018.02.023, indexed in Pubmed: 29650125.
6. Ijichi T, Nakazawa G, Torii S, et al. Comparisons of early vascular reactions in biodegradable and durable polymer-based drug-eluting stents in the porcine coronary artery. PLoS One. 2019; 14(1): e0209841, doi: 10.1371/journal.pone.0209841, indexed in Pubmed: 30629613.
7. Urban P, Meredith IT, Abizaid A, et al. Polymer-free drug-coated coronary stents in patients at high bleeding risk. N Engl J Med. 2015; 373(21): 2038–2047, doi: 10.1056/NEJMoa1503943, indexed in Pubmed: 26466021.
8. Song SJ, Jung K, Park Y, et al. Nitrogen-doped TiO2 films as drug-binding matrices for the preparation of drug-eluting stents. J Mater Chem. 2011; 21(22): 8169–8177, doi: 10.1039/c0jm03994b.
9. Song SJ, Park Y, Park J, et al. Preparation of a drug-eluting stent using a TiO2 film deposited by plasma enhanced chemical vapour deposition as a drug-combining matrix. J Mater Chem. 2010; 20(23): 4792–4801, doi: 10.1039/b925409a.
10. Park DS, Bae IH, Jeong MHo, et al. In vitro and in vivo evaluation of a novel polymer-free everolimus-eluting stent by nitrogen-doped titanium dioxide film deposition. Mater Sci Eng C Mater Biol Appl. 2018; 91: 615–623, doi: 10.1016/j.msec.2018.05.064, indexed in Pubmed: 30033294.
11. Sim DS, Jeong MHo, Park DS, et al. A novel polymer-free drug-eluting stent coated with everolimus using nitrogen-doped titanium dioxide film deposition in a porcine coronary restenosis model. Int J Cardiol. 2016; 222: 436–440, doi: 10.1016/j.ijcard.2016.07.275, indexed in Pubmed: 27505330.
12. Won H, Kim JS, Shin DH, et al. Serial changes of neointimal tissue after everolimus-eluting stent implantation in porcine coronary artery: an optical coherence tomography analysis. Biomed Res Int. 2014; 2014: 851676, doi: 10.1155/2014/851676, indexed in Pubmed: 25309929.
13. Byrne RA, Mehilli J, Iijima R, et al. A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents. Eur Heart J. 2009; 30(8): 923–931, doi: 10.1093/eurheartj/ehp044, indexed in Pubmed: 19240066.
14. Massberg S, Byrne RA, Kastrati A, et al. Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISAR-TEST 5) trial. Circulation. 2011; 124(5): 624–632, doi: 10.1161/CIRCULATIONAHA.111.026732, indexed in Pubmed: 21768546.
15. Kufner S, Sorges J, Mehilli J, et al. Randomized trial of polymer-free sirolimus- and probucol-eluting stents versus durable polymer zotarolimus-eluting stents: 5-year results of the ISAR-TEST-5 trial. JACC Cardiovasc Interv. 2016; 9(8): 784–792, doi: 10.1016/j.jcin.2016.01.009, indexed in Pubmed: 27017366.
16. Torii S, Cheng Qi, Mori H, et al. Acute thrombogenicity of fluoropolymer-coated versus biodegradable and polymer-free stents. EuroIntervention. 2019; 14(16): 1685–1693, doi: 10.4244/EIJ-D-17-00728, indexed in Pubmed: 29619983.
17. Otsuka F, Cheng Qi, Yahagi K, et al. Acute thrombogenicity of a durable polymer everolimus-eluting stent relative to contemporary drug-eluting stents with biodegradable polymer coatings assessed ex vivo in a swine shunt model. JACC Cardiovasc Interv. 2015; 8(9): 1248–1260, doi: 10.1016/j.jcin.2015.03.029, indexed in Pubmed: 26292590.
18. Chen W, Habraken TCJ, Hennink WE, et al. Polymer-Free drug-eluting stents: an overview of coating strategies and comparison with polymer-coated drug-eluting stents. Bioconjug Chem. 2015; 26(7): 1277–1288, doi: 10.1021/acs.bioconjchem.5b00192, indexed in Pubmed: 26041505.
19. De Scheerder I, Verbeken E, Van Humbeeck J. Metallic surface modification. Semin Interv Cardiol. 1998; 3(3-4): 139–144.
20. Dibra A, Kastrati A, Mehilli J, et al. Influence of stent surface topography on the outcomes of patients undergoing coronary stenting: a randomized double-blind controlled trial. Catheter Cardiovasc Interv. 2005; 65(3): 374–380, doi: 10.1002/ccd.20400, indexed in Pubmed: 15926182.
21. Palmaz JC, Benson A, Sprague EA. Influence of surface topography on endothelialization of intravascular metallic material. J Vasc Interv Radiol. 1999; 10(4): 439–444, doi: 10.1016/s1051-0443(99)70063-1, indexed in Pubmed: 10229473.
22. Kolandaivelu K, Bailey L, Buzzi S, et al. Ultra-hydrophilic stent platforms promote early vascular healing and minimise late tissue response: a potential alternative to second-generation drug-eluting stents. EuroIntervention. 2017; 12(17): 2148–2156, doi: 10.4244/EIJ-D-15-00497, indexed in Pubmed: 27993749.
23. Hezi-Yamit A, Sullivan C, Wong J, et al. Impact of polymer hydrophilicity on biocompatibility: implication for DES polymer design. J Biomed Mater Res A. 2009; 90(1): 133–141, doi: 10.1002/jbm.a.32057, indexed in Pubmed: 18491390.
24. Habib A, Karmali V, John MC, et al. Everolimus-eluting stents improve vascular response in a diabetic animal model. Circ Cardiovasc Interv. 2014; 7(4): 526–532, doi: 10.1161/CIRCINTERVENTIONS.113.001023, indexed in Pubmed: 24915972.
25. Buiten R, Ploumen E, Zocca P, et al. Thin, very thin, or ultrathin strut biodegradable or durable polymer-coated drug-eluting stents. JACC: Cardiovasc Interv. 2019; 12(17): 1650–1660, doi: 10.1016/j.jcin.2019.04.054.
26. Jensen LO, Thayssen P, Christiansen EH, et al. Safety and efficacy of everolimus- versus sirolimus-eluting stents: 5-year results from SORT OUT IV. J Am Coll Cardiol. 2016; 67(7): 751–762, doi: 10.1016/j.jacc.2015.11.051, indexed in Pubmed: 26892409.
27. Cho KH, Jeong MHo, Park DS, et al. Preclinical evaluation of a novel polymer-free everolimus-eluting stent in a mid-term porcine coronary restenosis model. J Korean Med Sci. 2021; 36(40): e259, doi: 10.3346/jkms.2021.36.e259, indexed in Pubmed: 34664799.