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Cardiovascular Disorders



First-in-Human Evaluation of a Polymer-Free Everolimus-Eluting Stent Using a Titanium Dioxide Film

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ABSTRACT

Background: In patients with coronary artery disease treated with permanent polymer-coated drug-eluting stents (DES), the persistent presence of a less biocompatible polymer might delay arterial healing. Thin strut polymer-free DES have the potential to improve clinical outcomes and reduce the duration of dual antiplatelet therapy (DAPT). The purpose of this first-in-human study was to assess the safety and effectiveness of a novel polymer-free DES in patients with de novo coronary lesions. The TIGERevolutionN[®] stent (CG Bio Co., Ltd., Seoul, Korea) consists of a cobalt chromium platform with a strut thickness of 70 µm and a surface treated with titanium dioxide onto which everolimus-eluting stent (EES) is applied abluminally (6 µg/mm of stent length) without utilization of a polymer.

Methods: A total of 20 patients were enrolled, with de novo coronary lesions (stable or unstable angina) and > 50% diameter stenosis in a vessel 2.25 to 4.00 mm in diameter and ≤ 40 mm in length for angiographic, optical coherence tomography (OCT), and clinical assessment at 8 months. All patients received DAPT after stent implantation. The primary endpoint was angiographic in-stent late lumen loss (LLL) at 8 months.

Results: Twenty patients with 20 lesions were treated with TIGERevolutionN[®]. At 8 months, in-stent LLL was 0.7 ± 0.4 mm. On OCT, percent area stenosis was 29.2 ± 9.4% and stent strut coverage was complete in all lesions. No adverse cardiovascular event occurred at 8 months.

Conclusion: The new polymer-free EES was safe and effective with low LLL and excellent strut coverage at 8 months of follow-up.

Trial Registration: Clinical Research Information Service Identifier: [KCT0005699](https://cris.nih.gov/KCT0005699)

Keywords: Drug-Eluting Stents; Titanium Dioxide; Polymers

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Disclosure

The authors have no potential conflicts of interest to disclose.

Data Sharing Statement

Data sharing statement is provided in
Supplementary Data 1.

Author Contributions

Conceptualization: Cho KH, Park JK, Byeon DH, Jeong MH. Data curation: Hyun DY, Kim SW, Ahn JH, Lee SH, Kim MC, Hong YJ, Kim JH, Ahn Y. Formal analysis: Sim DS, Kim SW. Funding acquisition: Jeong MH. Investigation:

INTRODUCTION

Compared to bare-metal stents, drug-eluting stents (DES) have significantly reduced restenosis rates after percutaneous coronary intervention (PCI).¹⁻³ However, DES treatment has limitations of delayed arterial healing and late stent thrombosis,⁴ which may be associated with polymers used for drug coating.⁵⁻⁷ Therefore, a polymer-free stent may prevent the deleterious effects induced by polymers such as inflammation and thrombosis, and potentially enable a shorter dual anti platelet therapy (DAPT) duration and improved clinical outcome.⁸

The TIGERevolution[®] (CG Bio Co., Ltd., Seoul, Korea) is a new, polymer-free, cobalt chromium thin-strut (70 μ m), coronary everolimus-eluting stent (EES) using titanium dioxide (TiO₂) thin film designed to improve arterial healing by obviating problems caused by the interaction between the polymer and the vessel wall (Fig. 1).

The primary objectives of this first-in-human study were to provide a preliminary assessment of the safety and efficacy of the TIGERevolution[®] in patients with de novo coronary artery disease and to provide guidance for future randomized study designs. We herein report the results of angiographic and optical coherence tomography (OCT) imaging evaluation, as well as clinical outcomes at 8 months of follow-up from the clinical experience with the TIGERevolution[®] stent.

METHODS

Device description

The study device has been described in detail elsewhere.^{9,10} Briefly, the TIGERevolution[®] is a polymer-free DES that consists of a cobalt chromium stent platform with a thin strut (70 μ m) and a surface treated with TiO₂ thin film, which allows adhesion of everolimus to the abluminal surface of the stent without a polymer by forming ester bonds between hydroxyl groups on the TiO₂ film and carboxyl groups in the drugs (Fig. 1).^{11,12} This “method for manufacturing of drug-releasing stent coated with titanium-oxide thin film” was granted a United States patent (No. US 8,999,456 B2). The drug dose is 6 μ g/mm of stent length. After stent implantation approximately 50% of everolimus is eluted within 15 days, approximately

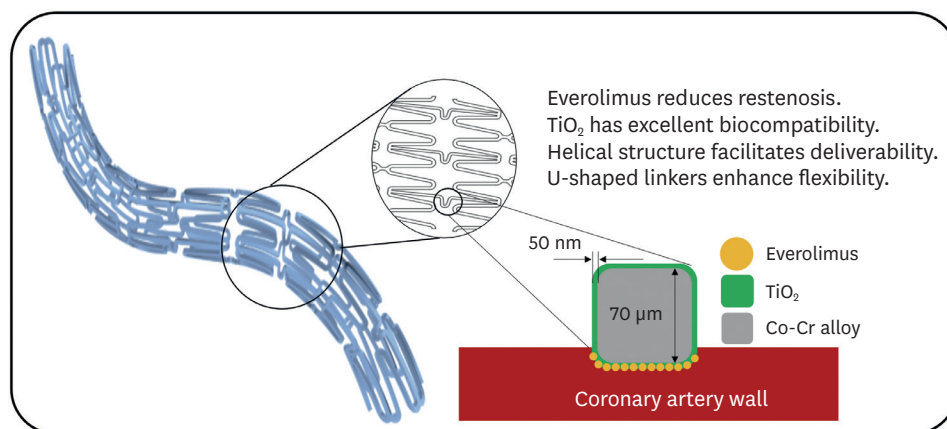


Fig. 1. Construction and properties of the TIGERevolution[®] polymer-free stent. TiO₂ = titanium dioxide, Co-Cr = cobalt chromium.

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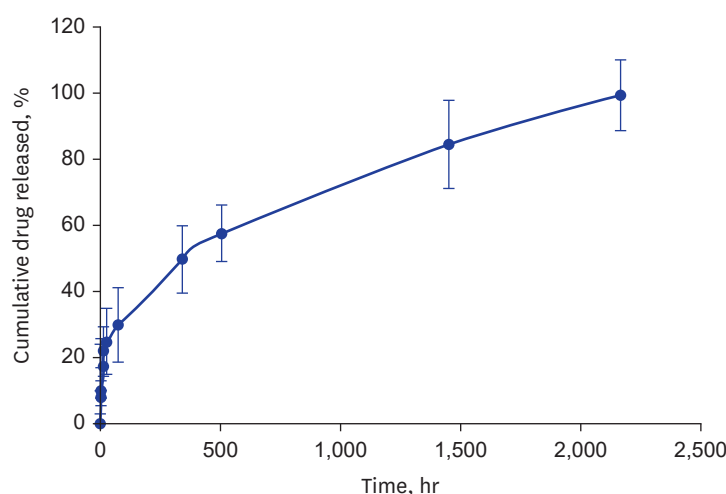


Fig. 2. In vitro release kinetics of everolimus from the TIGERevolutionN® stent (courtesy of CG Bio Co., Ltd., Seoul, Korea).

85% within 60 days and drug elution is complete by 90 days (Fig. 2). The TIGERevolutionN® stents were available in 3.0–4.0 mm diameters and 18–33 mm lengths in this study.

Study design and population

A total of 20 patients were enrolled at a single center in South Korea to evaluate the clinical safety and efficacy of this polymer-free EES for the treatment of de novo coronary lesions. Patients were included if they were > 19 years old, had typical symptoms and a single vessel disease with > 50% stenosis on coronary angiography or a single target vessel determined by a fractional flow reserve value < 0.8 in case of multivessel disease. Treatment was permitted in a single target native coronary artery with a reference vessel diameter between 2.25 and 4.0 mm and length ≤ 40 mm with thrombolysis in myocardial infarction (MI) flow grade ≥ 1 on baseline coronary angiography. Key exclusion criteria were acute MI, cardiogenic shock, chronic total occlusion, an unprotected left main lesion, a target lesion in a bypass graft, previous stenting in the target vessel, lesion location within 3 mm of the origin of the left anterior descending, left circumflex or right coronary artery, left ventricular ejection fraction < 40% within 6 months prior to procedure by echocardiography, estimated glomerular filtration rate < 30 mL/min/1.73m² or on renal replacement therapy, known hypersensitivity or contraindication to antithrombotic therapy, and life expectancy < 12 months. The full list of inclusion and exclusion criteria can be accessed at cris.nih.go.kr (KCT0005699). All patients underwent baseline medical assessment, and the implantation of TIGERevolutionN® stent was performed according to the standard PCI procedures. After pre-dilation of the lesion, the stent was expanded using a semi-compliant balloon. Angiographic and OCT data were collected and clinical outcomes were evaluated over 8 months as described below.

Stenting procedure

The length of the TIGERevolutionN® stent should be sufficient to cover the lesion with one stent or maximum two overlapping stents, and the size of the stent should match the diameter of the reference vessel with the stent to vessel ratio of 1.0–1.1 to 1. Post-dilatation after stenting was conducted at the discretion of the operator using a non-compliant balloon. OCT was performed to guide PCI in decision-making before and after stent deployment. After stenting, DAPT was recommended for at least 6 months in all patients and for up to 12 months in patients deemed not at high bleeding risk at the discretion of the treating physician.

Angiographic analysis

Serial coronary angiographic images were obtained after intracoronary nitroglycerin (100 to 200 µg, unless contraindicated) in 2 orthogonal matching views at pre-PCI, post-PCI and follow-up at 8 months. Angiographic analysis was conducted by experienced operators who were blinded to data on the procedure and clinical outcome. Quantitative coronary analysis (QCA) was performed with dedicated 2-dimensional software (Centricity CA-1000; GE Healthcare, Little Chalfont, United Kingdom). QCA data were described as in-stent (within stent) and in-lesion (stent plus 5 mm proximal and distal to the stent).

OCT image acquisition and analysis

All OCT images were obtained with C7XR Fourier-Domain OCT System (St. Jude Medical, Minneapolis, MN, USA) and were analyzed with Echo Plaque 4.3.12 (INDEC Systems, Mountain View, CA, USA). Imaging acquisition procedures were previously described.¹³ Analysis of OCT images at 0.6-mm longitudinal intervals was conducted at an independent core laboratory (Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea). Neointimal hyperplasia (National Institutes of Health; NIH) area was defined as the area between the stent and lumen contours. The percentage of area stenosis area was defined as $(\text{NIH area}/\text{stent area}) \times 100$. For determination of strut malapposition of the TIGERevolutionN[®] stent, a cutoff of 90 µm was used (70 µm for strut thickness, 20 µm for the compensation factor to correct for strut blooming¹⁴). The percentage of uncovered struts was calculated as the number of uncovered struts divided by the total number of struts in each cross-section analyzed.

Study endpoints and definitions

The primary endpoint was angiographic in-stent late lumen loss (LLL) by QCA, defined as the difference minimal lumen diameter (MLD) in the same segment between post-PCI and 8-month follow-up. Secondary procedural endpoints were device success, determined as in-stent residual diameter stenosis < 50% by QCA with use of the TIGERevolutionN[®] stent; lesion success, as in-stent residual diameter stenosis < 50% by QCA with use of any percutaneous method; and procedural success, as a lesion success without in-hospital major adverse cardiac events (MACE), defined as the composite of death, MI, or repeat target vessel revascularization (TVR). Key secondary QCA endpoints at 8-month follow-up were in-lesion LLL, percentage of diameter stenosis, MLD, and binary restenosis ($\geq 50\%$ stenosis of the luminal diameter). Secondary OCT endpoints were percentage of uncovered struts; percentage of malapposed struts; percentage of incomplete strut apposition area; stent area and volume; lumen area and volume; and neointimal hyperplasia area and volume at 8 months.

The clinical secondary endpoints included MACE, MI, clinically driven TVR, and definite or probable stent thrombosis at 8 months. Deaths were considered cardiac unless an unequivocal noncardiac cause could be established. MI was defined according to the Society of Cardiac Angiography and Interventions definition for clinically relevant MI after coronary revascularization.¹⁵ Clinically driven TVR was defined as repeat revascularization of the target vessel in the presence of a positive result on a functional ischemia study or ischemic symptoms and an angiographic diameter stenosis $\geq 50\%$ determined by QCA, or revascularization of a target vessel with diameter stenosis $\geq 70\%$ by QCA in the absence of angina or functional ischemia. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium criteria.¹⁶

Follow-up visits and studies

Clinical follow-up was planned at 4, 12, and 32 weeks. All patients underwent clinical evaluation and repeat coronary angiography and OCT at 8 months.

Statistical analysis

The analyses were limited to descriptive statistics and reported as count and percentage for categorical variables and mean $\pm$ standard deviation for continuous variables. All analyses were conducted using SPSS version 21 (IBM Corp., Armonk, NY, USA).

Ethics statement

The present study was in accordance with the Declaration of Helsinki, followed International Organization for Standardization standard 14,155, and was approved by the institutional ethics committee. The approval number was CNUH-2020-364 of Chonnam National University Hospital. All patients provided written informed consent.

RESULTS

Study population and acute success

A total of 20 patients with 20 treated lesions were enrolled between April 2021 and October 2021. The mean patient age was 62.4 years, 85% were men, hypertension was present in 60%, diabetes in 35%, dyslipidemia in 75%, and 95% had unstable angina (**Table 1**). On coronary angiography 90% of the target lesions were American Heart Association/American College of Cardiology type B2 and 65% were present in the left anterior descending artery (**Table 2**). All PCI were performed through the radial artery route. All lesions were successfully treated and device success, lesion success and procedure success were all 100%. The mean stent diameter was 3.4 ± 0.4 mm and length 22.6 ± 6.2 mm. Post-dilatation using a non-compliant balloon was done in 18 patients (90%). All patients received aspirin and clopidogrel after PCI and throughout the study period (**Table 2**).

Angiographic outcomes

Eight-month outcomes were available for all 20 patients and 20 lesions. Eight-month angiographic outcomes are shown in **Table 3**. The primary endpoint, in-stent LLL, was 0.7 ± 0.4 mm at 8 months. In-stent MLD was 2.1 ± 0.5 mm and in-stent percent diameter stenosis $31.9 \pm 11.5\%$ at 8 months.

Table 1. Baseline characteristics

Variables	Total (N = 20)
Age, yr	62.4 $\pm$ 9.6
Men	17 (85.0)
Hypertension	12 (60.0)
Diabetes mellitus	7 (35.0)
Smoking	7 (35.0)
Dyslipidemia	15 (75.0)
Family history of CAD	1 (5.0)
Stroke	3 (15.0)
Chronic lung disease	1 (5.0)
Cancer	1 (5.0)
Clinical presentation	
Stable angina	1 (5.0)
Unstable angina	19 (95.0)

Values are presented as mean $\pm$ standard deviation or number (%).

CAD = coronary artery disease.

Table 2. Procedural characteristics and antiplatelet therapy

Variables	Total (N = 20)
Treated vessel	
Left anterior descending artery	13 (65.0)
Right coronary artery	7 (35.0)
Left circumflex artery	0 (0.0)
Radial artery access	20 (100.0)
Lesion complexity	
ACC/AHA lesion classification	
B1	2 (10.0)
B2	18 (90.0)
Bifurcation	0 (0.0)
Calcification	0 (0.0)
Thrombus	0 (0.0)
OCT	20 (100.0)
Fractional flow reserve	1 (5.0)
Device success	20 (100.0)
Lesion success	20 (100.0)
Procedural success	20 (100.0)
Pre-PCI TIMI flow grade	
0	0 (0.0)
1	3 (15.0)
2	13 (65.0)
3	4 (20.0)
Post-PCI TIMI flow grade	
0	0 (0.0)
1	0 (0.0)
2	0 (0.0)
3	20 (100.0)
Implanted stent per patient	
Number	1.0 ± 0.0
Diameter, mm	3.4 ± 0.4
Length, mm	22.6 ± 6.2
Non-compliant balloon post-dilation	18 (90.0)
Diameter, mm	3.5 ± 0.4
Length, mm	12.4 ± 2.4
Pressure, atm	20.4 ± 2.6
Antiplatelet therapy at discharge	
Aspirin	20 (100.0)
Clopidogrel	20 (100.0)

Values are presented as number (%) or mean ± standard deviation.

ACC/AHA = American College of Cardiology/American Heart Association, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, TIMI = thrombolysis in myocardial infarction.

Table 3. Results of quantitative coronary angiography

Variables	Post-procedure (n = 20)	8 mon (n = 20)
Reference vessel diameter, mm	3.22 ± 0.41	3.04 ± 0.40
Minimum luminal diameter, mm		
In-lesion	2.63 ± 0.42	2.07 ± 0.44
In-stent	2.78 ± 0.37	2.10 ± 0.49
Percentage of diameter stenosis		
In-lesion	18.29 ± 9.37	31.89 ± 11.51
In-stent	13.48 ± 7.77	31.02 ± 12.33
Late lumen loss, mm		
In-lesion	NA	0.55 ± 0.45
In-stent	NA	0.68 ± 0.45
Binary angiographic restenosis, %		
In-lesion	NA	0
In-stent	NA	0

Values are presented as mean ± standard deviation or number (%).

NA = not applicable.

Table 4. Results of optical coherence tomography

Variables	Post-procedure (n = 20)	8 mon (n = 20)
No. of analyzed struts	NA	217 ± 70
Uncovered stent struts, %	NA	0
Malapposed stent struts, %	NA	0.20 ± 0.74
Mean incomplete strut apposition area, mm ²	NA	0.02 ± 0.07
Stent volume, mm ³	152.93 ± 63.53	174.2 ± 81.9
Mean stent area, mm ²	7.25 ± 1.74	7.81 ± 2.51
Minimal stent area, mm ²	5.94 ± 1.52	6.40 ± 1.96
Lumen volume, mm ³	160.15 ± 62.34	128.39 ± 76.29
Mean lumen area, mm ²	7.70 ± 1.82	5.69 ± 2.56
Minimal lumen area, mm ²	6.11 ± 1.47	4.03 ± 2.00
Neointimal hyperplasia volume, mm ³	NA	46.14 ± 15.00
Mean neointimal hyperplasia area, mm ²	NA	2.13 ± 0.52
Maximum neointimal hyperplasia area, mm ²	NA	3.45 ± 0.90
Area stenosis, %	NA	29.17 ± 9.36

Values are presented as mean ± standard deviation or number (%).

NA = not applicable.

Table 5. Clinical outcomes at 8 months

Variables	Values
Death from any cause	0 (0.0)
Myocardial infarction	0 (0.0)
Repeat revascularization	0 (0.0)
Target vessel revascularization	0 (0.0)
Stent thrombosis	0 (0.0)
Stroke	0 (0.0)
Bleeding complications	0 (0.0)
Rehospitalization	0 (0.0)

Values are presented as number (%).

OCT outcomes

The percentage of covered struts per lesion at 8 month was 100% and the percentage of malapposed struts was 0.20 ± 0.74% at 8 months (**Table 4**). Mean NIH area was 2.1 ± 0.5 mm², mean NIH volume 46.1 ± 15.0 mm³, and percent area stenosis 29.2 ± 9.4% (**Table 4**). There were no cases of coronary aneurysm or intracoronary thrombus.

Clinical outcomes

The percentage of DAPT use at 8 months was 100%. There were no adverse clinical event including death, MI, target lesion or TVRs, stent thrombosis, stroke, or bleeding complications during the 8 months of follow-up (**Table 5**).

DISCUSSION

This first-in-human study with the novel polymer-free EES (TIGERevolutioN®) demonstrated low 8-month in-stent LLL. OCT revealed small NIH and excellent stent strut coverage with minimal malapposition, consistent with favorable arterial healing. At 8-month follow-up, no adverse clinical event occurred, nor were there any cases of stent thrombosis or binary angiographic restenosis. To our knowledge this is the first clinical validation of its kind to test the safety and efficacy of a thin-strut polymer-free DES incorporating a new drug combining technology utilizing a TiO₂ film.

Although second-generation DES compared to first-generation DES have reduced the risk of stent thrombosis and repeat revascularization,^{17,18} there remains a need for novel

devices that can lower the risk of ischemic events further as well as the dependence on DAPT following PCI. Despite the use of more sophisticated design of DES and more biocompatible materials in recent years, there is a risk of inflammation with all durable polymers, which may eventually contribute to neoatherosclerosis, late catch-up, and late stent thrombosis after stent placement.¹⁴ Therefore, DES platforms for drug delivery through bioabsorbable polymers or without polymers may hold the potential to reduce the risk of long-term adverse events associated with permanent polymers and decrease the need for prolonged DAPT. Polymer-free DES have been developed to address issues caused by interactions between the polymer and the vessel wall including inflammatory reactions as well as problems attributed to cracking or webbing of the polymer coating on stent expansion. In spite of theoretical benefits of polymer-free DES compared to current permanent-polymer DES,^{8,19-22} randomized trials have not yet demonstrated a clinical advantage.^{23,24} Further studies are required to find clinical scenarios where polymer-free DES may be advantageous to current permanent or bioabsorbable polymer DES. One of the challenges of polymer-free DES is to control the dose and elution kinetics of the drug properly during the early period after stenting without initial burst release. Attempts to tackle this issue have included stent surface modification for drug loading, use of more lipophilic drugs, or novel stent platforms designed for the drug to be effectively contained and eluted in a stable and sustained manner.²⁵

We recently developed a new drug combining method utilizing a TiO₂ film without a polymer to obviate problems arising from the interaction between the polymer and the vessel wall.^{12,26} Titanium is known to exhibit superior blood compatibility as compared with stainless steel or gold,²⁷ and TiO₂ coated on a metal stent promotes anticoagulation effect by inhibiting platelet adhesion and aggregation.²⁸ TIGERevolutionN[®] is a polymer-free DES that consists of a cobalt chromium alloy with a strut thickness of 70 µm and a surface treated with TiO₂ onto which everolimus is applied abluminally (Fig. 1).^{9,10} After implantation it shows stable drug release without an initial burst, approximately 85% of everolimus being eluted within 60 days and drug elution completed by 90 days (Fig. 2). This approach of drug delivery was aimed to promote tissue coverage of the stent struts while inhibiting inflammation and neointimal proliferation. Our previous preclinical studies with histological analysis in coronary restenosis porcine models demonstrated superior early and late reduction of neointimal proliferation with the TIGERevolutionN[®] stent compared with a commercial polymer-free sirolimus-eluting stent at 6 months.²⁹ In addition, there was superior arterial healing, as evidenced by rare fibrin deposit at 1 month and 6 months with the TIGERevolutionN[®] stent compared with commercial permanent-polymer EES and polymer-free sirolimus-eluting stent.^{9,10,29} Taken together, the present first-in-human study confirmed, up to 8 months, the preliminary safety and efficacy of the TIGERevolutionN[®] stent in de novo coronary artery lesions. The low angiographic in-stent LLL and the low area stenosis on OCT at 8-month follow-up suggest potent inhibition of NIH consistent with outcomes of current generation DES utilizing rapamycin-derivatives, notwithstanding the absence of a drug carrier.³⁰⁻³² Larger comparative clinical trials with long-term follow-up are warranted to examine whether these favorable results translate into improved clinical outcome and permit shorter DAPT duration, which would greatly benefit patient subsets at both high ischemic and bleeding risks.

There are several limitations to the present study. Firstly, our study has limitations that are inherent to a non-randomised first-in-human study. The sample size was small and not powered for clinical events. The lack of a direct comparison with other commercial stents restricts the interpretation of the results. In SPIRIT I,³³ the first-in-human study of the cobalt chromium EES with a permanent polymer (Xience V[®]; Abbott Vascular, Santa Clara,

CA, USA) in-stent LLL at 6 months in patients treated with Xience V® stent was 0.10 ± 0.21 mm significantly lower than that in bare-metal stent control (0.87 ± 0.37 mm, $P < 0.001$). Even though the LLL of Xience V® stent was numerically lower than that of TIGERevolutionN® stent used in our study, we cannot directly compare these two groups because they are quite different in baseline and procedural characteristics as well as inclusion criteria. In SPIRIT I trial³³ patients had lower risk profiles than those enrolled in our study, such as shorter lesion length (10.1 ± 2.6 mm lesion length vs 22.6 ± 6.2 mm stent length in our study); lower prevalence of diabetes (11% vs. 35%), unstable angina (19% vs. 95%) and lesion type B2 (59% vs. 90%); and shorter follow-up (6 months vs. 8 months in our study). We, therefore, feel it necessary to conduct a confirmatory randomized clinical trial comparing our TIGERevolutionN® stent with a contemporary permanent polymer EES for a long-term follow-up to prove the potential benefits our polymer-free DES possess. Secondly, only patients with de-novo lesions, relatively short and not severely stenotic, were included and higher risk patients, such as those with acute MI, left main lesion, or cardiogenic shock were excluded. Thus, our results are hypothesis-generating and cannot be generalized to other types of complex lesions. Thirdly, the follow-up period of 8 months was relatively short to assess long-term safety and efficacy including late catch-up of DES and very late stent thrombosis. Finally, serial healing between different time points by imaging studies was not addressed. Hence, early stent strut coverage assessment, which could be one of polymer-free DES' merits, was not available.

In conclusion, this first-in-human study of the TIGERevolutionN® in patients with de novo coronary artery lesions revealed low LLL and excellent strut coverage with minimal malapposition at 8 months of follow-up. There were no stent-related adverse clinical events. These promising results should be validated in future randomized clinical trials.

SUPPLEMENTARY MATERIAL

Supplementary Data 1

Data sharing statement

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