International Journal of Nanomedicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Long-Term Clinical Outcomes of Polymer-Free Sirolimus-Eluting Stent and Polymer-Coated Sirolimus-Eluting Stent in Patients with Type 2 Diabetes

Ou Yang[1], Yuhuan Teng[1], Ruoxi Zhang[2], Jie Qu[1]

[1]Department of Cadre Ward, The First Hospital of Jilin University, Changchun, Jilin, 130021, People's Republic of China; [2]Department of Cardiology, Harbin Yinghua Hospital, Harbin, Heilongjiang, 150199, People's Republic of China

Correspondence: Jie Qu; Ruoxi Zhang, Email qj610714@jlu.edu.cn; ruoxizhang8@qq.com

Introduction: Polymer-free sirolimus-eluting stent (PF-SES) possess multiple properties improving targeted drug elution and in-stent reendothelialization without the presence of polymers. The long-term clinical performance comparison between PF-SES and the latest generation polymer-coated sirolimus-eluting stents (SES), particularly regarding intravascular imaging assessment and in the type 2 diabetes mellitus (DM) population, remains unexplored.

Methods: We conducted a retrospective study involving 2646 diabetes patients meeting coronary artery disease (CAD) criteria underwent coronary stents in the real-world. All patients were divided into the PF-SES group and the SES group. Optical coherence tomography (OCT) was used to evaluate the imaging characteristics of in-stent reendothelialization. Patient information between the two groups was systematically compared in hospital and at 5-year follow-up.

Results: In terms of basic characteristics, the proportion of current smoker and stable angina patients in the PF-SES group was significantly higher than that in the SES group. The PF-SES group exhibited significantly higher rate of left anterior descending (LAD) lesion and more stents per patients compared to the SES group. The value of minimum lumen area (MLA), neointimal area (NA) and neointimal thickness (NT) were higher in the PF-SES group. Additionally, the occurrence rates of heterogeneous, lipid layer, intimal tears, thrombi, and micro-vessels were notably lower in the PF-SES group compared to the SES group. A higher all-cause mortality was observed in the SES cohort.

Discussion: PF-SES could effectively improve in-stent reendothelialization in patients with type 2 DM, with positive effects on survival rate and may, therefore, be considered as an alternative treatment option for improving clinical long-term outcomes.

Keywords: Polymer-free, polymer-coated, Nano Plus stent, drug-eluting stents, type 2 diabetes mellitus, optical coherence tomography

Introduction

Since the advent of drug-eluting stents (DES), significant advancements have been achieved in the management of coronary artery disease. The replacement of bare-metal stents with DES in standard clinical practice has led to noticeable decreases in in-stent restenosis and target lesion revascularization.[1] However, it has been observed that DES carry a heightened risk of late stent thrombosis due to delayed reendothelialization.[2,3] The durable polymer has been shown to cause vessel wall inflammation and hinder arterial healing, potentially increasing the risk of late thrombosis.[4,5] Polymer-free technologies have since emerged, with polymer-free DES designed to prevent adverse events resulting from hypersensitivity reactions and chronic inflammation associated with polymers.[6,7]

It is important to note that inflammation is considered a contributing factor in the development of type 2 diabetes mellitus (DM). A growing body of evidence indicates that inflammation plays a critical intermediary role in its pathogenesis. Substantial experimental data and extensive cross-sectional studies suggest that interleukin 6 (IL-6) and

Received: 13 June 2024
Accepted: 6 November 2024
Published: 11 November 2024

C-reactive protein (CRP), sensitive markers of sub-clinical systemic inflammation, are linked to hyperglycemia, insulin resistance, and overt type 2 DM.[8,9]

Therefore, we hypothesize that in diabetic patients experiencing heightened inflammation, the use of polymer-coated stents may worsen the inflammatory response. This, in turn, could impede vascular reendothelialization after stent implantation, ultimately affecting clinical outcomes. This study aimed to evaluate the long-term clinical outcomes of polymer-free sirolimus-eluting stents (PF-SES) in comparison to polymer-coated sirolimus-eluting stents (SES) in patients with type 2 DM.

Methods

Patient Population

This retrospective analysis included 2646 consecutive diabetes patients with coronary artery disease (CAD) who underwent coronary stents at The First Bethune Hospital of Jilin University. Patients were divided into two groups according to the type of coronary stents they received: PF-SES and SES (Figure 1). Patients diagnosed with type 2 DM were eligible for inclusion if they exhibited clinical symptoms of ischemia, indicating the presence of coronary artery stenosis necessitating the use of coronary stents.[10] The eligibility criteria for patient inclusion: (i) confirmed diagnosis of type 2 DM; (ii) presence of clinical symptoms of ischemia; (iii) evidence of coronary artery stenosis; and (iv) indication for coronary stent placement due to ischemic symptoms and stenosis. The exclusion criteria included: (i) pregnant women; (ii) left main trunk lesions; and (iii) any chronic illnesses such as cancer, liver cirrhosis, heart failure, or end-stage renal failure. Type 2 diabetes can be diagnosed if any of the following criteria is met:[11] (i) fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L); or (ii) 2-h PG ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT); or (iii) A1C ≥6.5% (48 mmol/mol); or (iv) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Study Device

The PF-SES used in our study is the Nano Plus stent, a new type of polymer-free sirolimus-eluting stent developed by Lepu Medical in Beijing, China. This stent employs nanoporous surface technology to carry and control drug release. The stent's abluminal surface features uniformly distributed nano-sized pores with an average diameter of 400 nm, which is 1/800th of the stent thickness (Figure 2A–C). The control stent used was the commercially available PARTNER stent, a self-expanding nitinol stent with a polymer-coated sirolimus delivery system (Figure 2a–c).

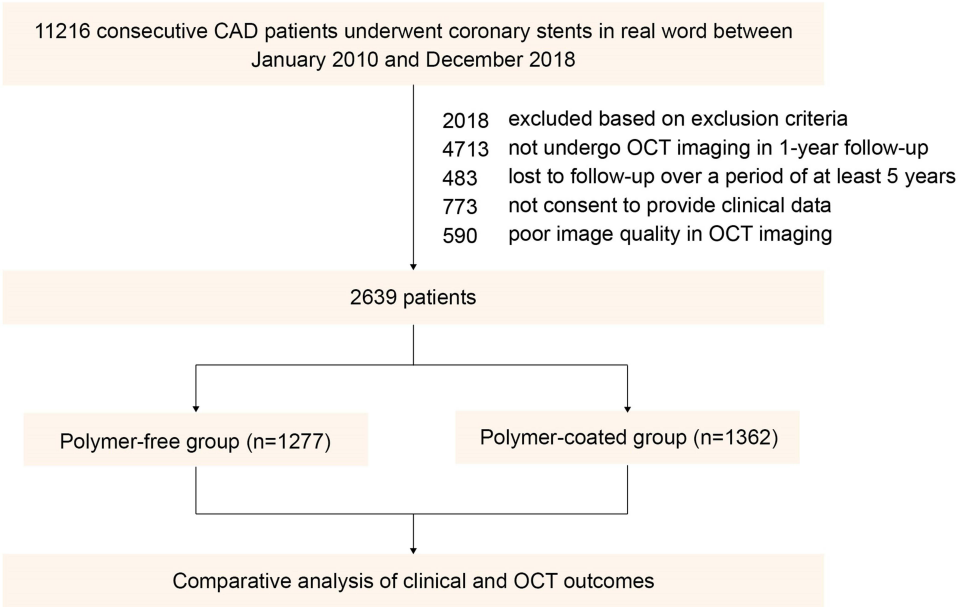


Figure 1 Flow chart of patients we analyzed in the present study.

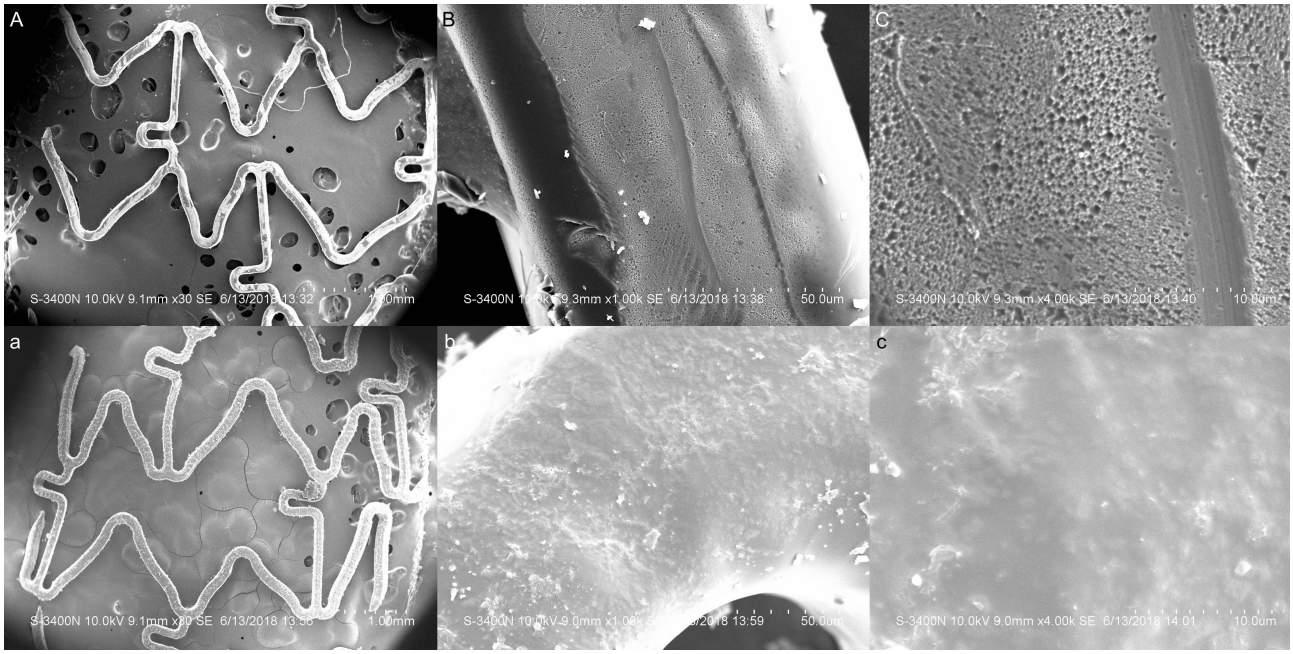


Figure 2 Scanning electron microscopy of stent surface between polymer-free sirolimus-eluting stent and polymer-coated sirolimus-eluting stent. (**A**–**C**) The magnification of polymer-free sirolimus-eluting stent is 30×, 1000× and 4000×, respectively; (**a**–**c**) The magnification of polymer-coated sirolimus-eluting stent is 30×, 1000× and 4000×, respectively.

The Nano Plus stents is manufactured by Lepu Medical Technology, a leading company in the medical device industry. These stents are designed to provide optimal performance for coronary interventions. The stents are available in various lengths ranging from 12 mm to 36 mm with diameter options of 2.5 mm to 4.0 mm, ensuring a wide range of applicability for different patient needs.

Key manufacturing features of the Nano Plus stents include:

(i) Material Composition: The stents are made from cobalt-chromium alloy, which offers a balance of strength and flexibility while minimizing the risk of restenosis.

(ii) Coating Technology: These stents utilize advanced drug-eluting technology with a biodegradable polymer coating to ensure controlled drug release, enhancing the healing process and reducing the likelihood of thrombosis.

(iii) Precision Engineering: The stents are engineered using laser-cutting techniques to ensure precision and consistency in stent design, promoting optimal deployment and integration within the coronary arteries.

(iv) Quality Control: Each stent undergoes rigorous quality control processes, including in-vitro and in-vivo testing, to ensure they meet stringent safety and efficacy standards.

For more detailed information on the product specifications and benefits, you can refer to the following link: https://pdf.medicalexpo.com.cn/pdf-en/lepu-medical/coronary-stent-nano/95737-263490.html#open657723.

The Partner stents are manufactured by Lepu Medical Technology, a renowned company in the medical device industry. These stents are designed to offer superior performance in coronary interventions. The stents come in a variety of lengths from 12 mm to 36 mm and are available in diameters ranging from 2.5 mm to 4.0 mm, ensuring they can meet a wide range of patient needs.

Key manufacturing features of the Partner stents include:

(i) Flexible Stent Design: The Partner stents incorporate a sine wave pattern with a 3-3-3 link and a double helix structure, providing flexibility and strength.

(ii) Balanced Strut Thickness: The stents have an optimized strut thickness that balances radial force and flexibility, ensuring effective support and minimal vessel injury.

(iii) High Radial Force: They provide high radial force for excellent vessel scaffolding, reducing the risk of stent collapse.

(iv) Large Open Cell Design: This design allows for optimal blood flow and facilitates access to side branches during procedures.

(v) Precise Positioning Markers: The stents are equipped with markers that enable accurate positioning during deployment.

(vi) Ultra Smooth Surface: The stents feature an ultra-smooth surface that minimizes friction and facilitates easy placement.

(vii) Double Layer Polymer Coating: The stents are coated with a double layer of polymer that enhances biocompatibility and drug delivery.

(viii) Sirolimus Drug Coating: Coated with Sirolimus, the stents provide controlled drug release over a 90-day period, promoting healing and reducing restenosis.

For more detailed information on the product specifications and benefits, you can refer to the following link: https://pdf.medicalexpo.com.cn/pdf-en/lepu-medical/coronary-stent-partner/95737-263492.html#open657726.

Coronary Angiography and Stenting

All primary coronary angiography and stenting were conducted at The First Bethune Hospital of Jilin University, by experienced interventional cardiologists with an annual experience for over 500 cases of percutaneous coronary intervention (PCI). These cardiologists were not associated with the current study. Baseline demographics, angiographic characteristics, as well as laboratory and physical examination data during hospitalization, were systematically documented by reviewing the patients' medical records.[12]

Coronary stenting was performed in accordance with the current standard of practice.[13] Revascularization strategies and stent implantation techniques were performed at the operator's discretion.[14] All patients were pretreated with aspirin and a P_2Y_{12} inhibitor (clopidogrel or ticagrelor) according to the standard of care and provided DAPT for at least 12 months according to the guidelines.[15] The continuation of DAPT beyond the duration of the recommended guidelines was performed at the physician's discretion. Additional medications for secondary prevention, including statins, beta-blockers, and angiotensin-converting enzyme inhibitors, were prescribed according to the guidelines.[13]

OCT Imaging and Analysis

The intracoronary imaging technique of optical coherence tomography (OCT) was previously outlined.[16] In the present study, either a frequency-domain OCT system (C7-XR OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA) was utilized. All OCT images were digitally stored and forwarded to the core laboratories of intracoronary imaging at THE FIRST BETHUNE HOSPITAL OF JILIN UNIVERSITY (Changchun, China) for offline analyses. In summary, within the frequency domain OCT system, a 2.7 F OCT imaging catheter (Dragonfly, Light Lab Imaging, Inc) was advanced at least 10 mm distal to the imaging target lesion. OCT image acquisition was then performed with automatic pullback (20 mm per second) and continuous intracoronary contrast injection. Each OCT catheter pullback imaged a total of 54 mm of the vessel.

Assessment of atherosclerosis involved identifying the presence of lipids and plaque microstructure (Figure 3). Lipid plaques were characterized as signal-poor areas with diffuse borders.[17] A plaque was deemed lipid-rich if lipid was present in ≥90 degree in any cross-sectional image within the plaque.[18] The fibrous cap thickness of the lipid plaque was measured three times at its thinnest part, and the values were averaged.[19] Thin cap fibroatheroma (TCFA) was defined as a plaque with a maximum lipid arc of >90 degrees and a cap thickness <65 μm. Micro-vessel were identified as sharply delineated signal-poor voids with a diameter of 50–300 μm, not connected to the vessel lumen, and present on >3 consecutive frames.[20]

Follow-Up

Patients were contacted by telephone or during a scheduled outpatient clinic visit arranged by their physicians. Follow-up data were collected up to 5 years post-procedure.

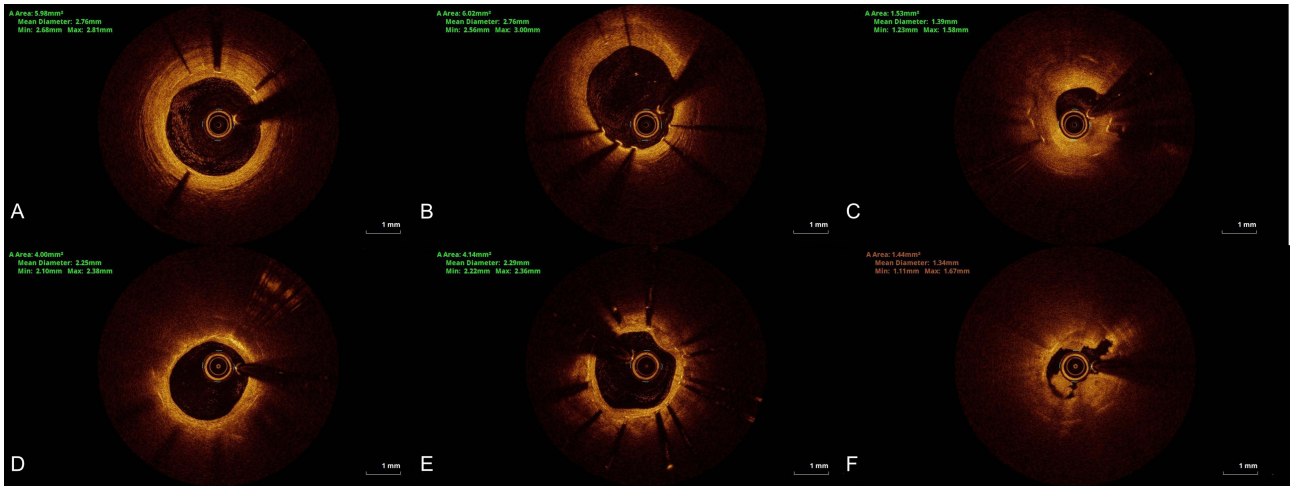


Figure 3 Representative cases with each tissue morphologies in stents assessed with OCT. OCT, optical coherence tomography. (**A**) Complete endothelial coverage on the surface of the stent; (**B**) Incomplete endothelial coverage on the surface of the stent; (**C**) In-stent neo-atherosclerosis; (**D**) Lipid-laden intima is observed as a signal-poor band region with poorly delineated border; (**E**) In-stent calcified plaque; (**F**) In-stent thrombosis.

Statistical Analysis

Quantitative data are expressed as the mean value ± standard deviation, while qualitative data are expressed as frequency (percentage). The independent two-sample *t*-test was used for comparisons between cohorts. The chi-square test or Fisher's exact test was used to compare categorical variables, as applicable. To estimate survival status, the Kaplan Meier (KM) technique was utilized, and the Log rank test was used to compare survival distributions. Two-sided *P*-values of <0.05 were deemed statistically significant. SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) was used to conduct all statistical analyses.

Results

Baseline Characteristics

In terms of basic characteristics, the proportion of current smoker (37.0% vs 32.0%, $P = 0.008$) in the PF-SES group was significantly higher than that in the SES group (Table 1). Among different types of CAD patients, the proportion of patients with stable angina in the PF-SES cohort is significantly higher than in the SES cohort (71.3% vs 64.4%, $P < 0.001$), while the proportion of patients with unstable angina (15.3% vs 20.2%, $P = 0.001$) and ST-elevation myocardial infarction (STEMI) in the PF-SES cohort (5.2% vs 8.3%, $P = 0.002$) is significantly lower (Table 1).

Table 1 Basic Characteristics in Patients

	PF-SES (n=1277)	SES (n=1369)	*P*-value
Age (years)	64.0 (6.2)	63.9 (5.9)	0.734
Female sex	503 (39.4)	517 (37.8)	0.401
BMI (kg/m^2)	26.1 (3.0)	25.8 (3.0)	0.032
Cardiovascular risk factors			
Hypertension	826 (64.7)	858 (62.7)	0.293
Hyperlipidemia	768 (60.1)	831 (60.7)	0.781
Current smoking	472 (37.0)	438 (32.0)	0.008
Previous MI	135 (10.6)	146 (10.7)	0.950
Previous PCI	122 (9.6)	131 (9.6)	1.000

(*Continued*)

Table 1 (Continued).

	PF-SES (n=1277)	SES (n=1369)	*P*-value
Types of CAD			
SA	910 (71.3)	881 (64.4)	< 0.001
UA	195 (15.3)	277 (20.2)	0.001
NSTEMI	92 (7.2)	84 (6.1)	0.275
STEMI	80 (5.2)	113 (8.3)	0.002
SBP (mmHg)	119.8 (19.4)	120.2 (19.5)	0.600
DBP (mmHg)	73.1 (14.1)	72.8 (13.7)	0.634
Mean troponin I (μg/L)	0.05 (0.05, 0.06)	0.05 (0.04, 0.06)	0.620
Mean CK-MB (μg/L)	17.0 (16.0, 19.0)	17.0 (16.0, 19.0)	0.573
ALT (U/L)	28.5 (10.4)	27.9 (11.1)	0.116
Creatinine (μmol/L)	78.5 (16.0)	78.2 (15.9)	0.625
HbA1c (%)	8.88 (1.23)	8.80 (1.18)	0.118
NT-proBNP (pg/mL)	99.0 (87.0–113.0)	100.0 (88.0–113.0)	0.686
CRP (mg/L)	20.89 (4.98)	20.86 (5.20)	0.898
Total cholesterol (mol/L)	4.51 (0.78)	4.52 (0.81)	0.818
LDL-cholesterol (mol/L)	3.07 (1.09)	3.03 (1.09)	0.449
HDL-cholesterol (mol/L)	1.29 (0.48)	1.31 (0.49)	0.175
Triglyceride (mol/L)	2.17 (0.95)	2.22 (0.96)	0.239
LVEF (%)	51.0 (2.0)	51.0 (2.0)	0.966
Medications at discharge			
Aspirin	1265 (99.1)	1356 (99.1)	1.000
Clopidogrel	708 (55.4)	867 (63.3)	< 0.001
Ticagrelor	569 (44.6)	502 (36.7)	< 0.001
Statin	1255 (98.3)	1344 (98.2)	0.884
β-Blocker	1075 (84.2)	1125 (82.2)	0.177
ACEI/ARB	330 (25.8)	326 (23.8)	0.241
PPI	320 (25.1)	353 (25.8)	0.688

Note: Mean values (standard deviation), median (interquartile range), and % (n) were reported for variables, respectively.

Abbreviations: PF-SES, polymer-free sirolimus-eluting stent; BMI, body mass index; CAD, coronary artery disease; SA, stable angina, UA, unstable angina; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; DBP, diastolic blood pressure; CK-MB, creatine kinase-MB; ALT, alanine aminotransferase; HbA1c, hemoglobinA1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; ACEI angiotensin-converting enzyme inhibitor; ARB angiotensin receptor II blocker; PPI, proton pump inhibitor.

Angiographic Findings

The comparison of coronary angiography and stenting between two groups is shown in Table 2. The PF-SES group exhibited significantly higher rate of left anterior descending (LAD) lesion and more stents per patient compared to the SES group (46.4% vs 42.1%, $P = 0.026$).

OCT Findings

The OCT findings are listed in Table 3. The value of minimum lumen area (MLA), neointimal area (NA) and neointimal thickness (NT) was significantly larger in the PF-SES group ($P < 0.001$). When compared with the SES group, the PF-SES group had a lower prevalence of heterogeneous, lipid layer, intimal tears, thrombi and micro-vessels ($P < 0.001$).

Table 2 Coronary Angiography and Stenting Therapy

	PF-SES (n=1277)	SES (n=1369)	*P*-value
Targeted lesion localization			
LAD	593 (46.4)	576 (42.1)	0.026
LCX	290 (22.7)	319 (23.3)	0.746
RCA	388 (30.4)	443 (32.4)	0.276
Diagonal branch	66 (5.2)	69 (5.0)	0.930
Obtuse branch	35 (2.7)	48 (3.5)	0.267
Stents per patient	1.12 (0.40)	1.09 (0.35)	0.037
Femoral access	122 (9.6)	120 (8.8)	0.500
IABP	122 (9.6)	120 (8.8)	0.500
Angiography data			
MLD (mm)	0.896 (0.360)	0.903 (0.372)	0.610
Diameter stenosis (%)	80.2 (5.5)	80.6 (5.2)	0.143
Lesion length (mm)	18.2 (7.4)	18.1 (7.8)	0.782

Note: Mean values (standard deviation), median (interquartile range), and % (n) were reported for variables, respectively.
Abbreviations: PF-SES, polymer-free sirolimus-eluting stent; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; IABP, intra-aortic balloon pump.

Table 3 Optical Coherence Tomography Findings in Follow-Up

	PF-SES (n=1277)	SES (n=1369)	*P*-value
OCT quantitative data			
Stent area (mm^2)	6.47 (0.73)	6.48 (0.64)	0.568
MLA (mm^2)	5.97 (0.68)	5.35 (0.56)	< 0.001
NA (mm^2)	0.47 (0.05)	0.63 (0.08)	< 0.001
NT (mm)	0.054 (0.006)	0.078 (0.009)	< 0.001
OCT qualitative data			
Homogeneous	943 (73.8)	619 (45.2)	< 0.001
Heterogeneous	334 (26.2)	750 (54.8)	< 0.001
Lipid layer	135 (10.6)	410 (29.9)	< 0.001
Intimal tears	61 (4.8)	122 (8.9)	< 0.001
Thrombi	61 (4.8)	152 (11.1)	< 0.001
Micro-vessel	92 (7.2)	328 (24.0)	< 0.001

Note: Mean values (standard deviation), median (interquartile range), and % (n) were reported for variables, respectively.
Abbreviations: PF-SES, polymer-free sirolimus-eluting stent; OCT, optical coherence tomography; MLA, minimum lumen area; NA, neointimal area; NT, neointimal thickness; TCFA, thin-cap fibroatheroma.

Long Term Follow-Up

In 5-year follow-up, the all-cause mortality, in-stent restenosis (ISR) and target vessel revascularization (TVR) were considerably lower in the PF-SES cohort than in the SES cohort (6.4% vs 8.6%, $P = 0.033$ and 7.6% vs 9.9%, $P = 0.046$ and 12.4% vs 21.1%, $P < 0.001$; Table 4 and Figure 4).

Discussion

The Nano Plus stent is an innovative polymer-free stent featuring nano-sized pores that serve as drug carriers for the antiproliferative drug sirolimus. It is one of the most widely used DES in China. The Nano Plus stent, with its improved uniform distribution on the abluminal stent surface compared to microporous or textured rough surface stents, significantly differs from traditional SES in terms of the drug-eluting mechanism (Figure 5). To our knowledge, this is the first

Table 4 Clinical Outcomes in 5-Year Follow-Up

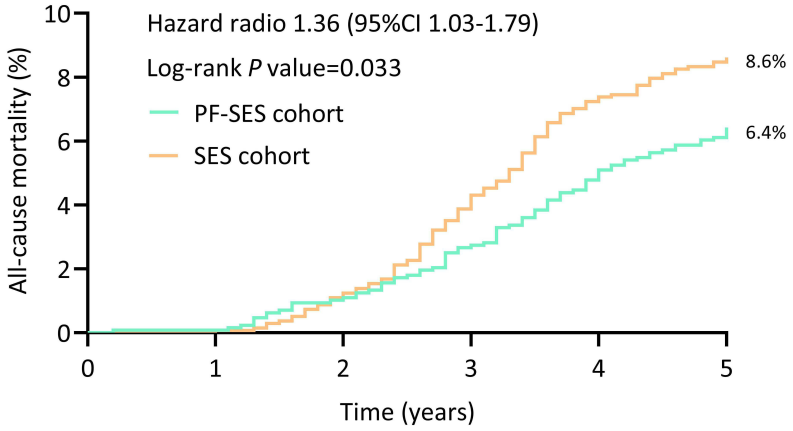
	PF-SES (n=1277)	SES (n=1369)	*P*-value
Clinic visits (times)	5.9 (1.0)	6.0 (1.0)	0.551
MACE			
All-cause mortality	82 (6.4)	118 (8.6)	0.033
Cardiovascular death	59 (4.6)	76 (5.6)	0.290
Non-fatal AMI	81 (6.3)	110 (8.0)	0.098
ISR	97 (7.6)	135 (9.9)	0.046
Stent thrombosis	50 (3.9)	62 (4.5)	0.441
TVR	158 (12.4)	290 (21.1)	< 0.001
Heart failure	139 (10.9)	167 (12.2)	0.301
Stroke	145 (11.4)	163 (11.9)	0.672
Re-hospitalization	329 (25.8)	325 (23.7)	0.241
New onset AF	143 (11.2)	162 (11.8)	0.626
New onset VA	121 (9.5)	157 (11.5)	0.099
New onset AVB	39 (3.1)	52 (3.8)	0.337

Note: Mean values (standard deviation), median (interquartile range), and % (n) were reported for variables, respectively.

Abbreviations: PF-SES, polymer-free sirolimus-eluting stent; MACE, major adverse cardiovascular event; AMI, acute myocardial infarction; ISR, in-stent restenosis; TVR, target vessel revascularization; AF, atrial fibrillation; VA, ventricular arrhythmias; AVB, advanced atrioventricular block.

study to demonstrate the safety and efficacy of PF-SES compared to SES assessed by OCT in CAD patients with type 2 DM for a long-term follow-up in real-world practice. The main findings were as follows. (i) PF-SES could effectively improve in-stent reendothelialization in patients with type 2 diabetes, (ii) positively impacting the survival rate. (iii) PF-SES may be considered an alternative treatment option for improving long-term clinical outcomes.

The traditional DES consists of three components: the stent, anti-proliferative drug, and the drug carrier.[21] The drug carrier is composed of one or more organic compounds forming a polymer.[22] It is coated onto the surface of the traditional metal stent along with anti-proliferative drug. The polymer material involved here refers to high molecular weight compounds formed by repetitive covalent bonding of many identical, simple structural units.[23] Typically, polymer coatings exhibit two main characteristics: serving as a reservoir for anti-proliferative drugs and determining the rate of



Number at risk

PF-SES cohort	1277	1277	1277	1243	1216	1199
SES cohort	1369	1369	1369	1316	1270	1253

Figure 4 All-cause mortality between two groups in 5-year follow-up.

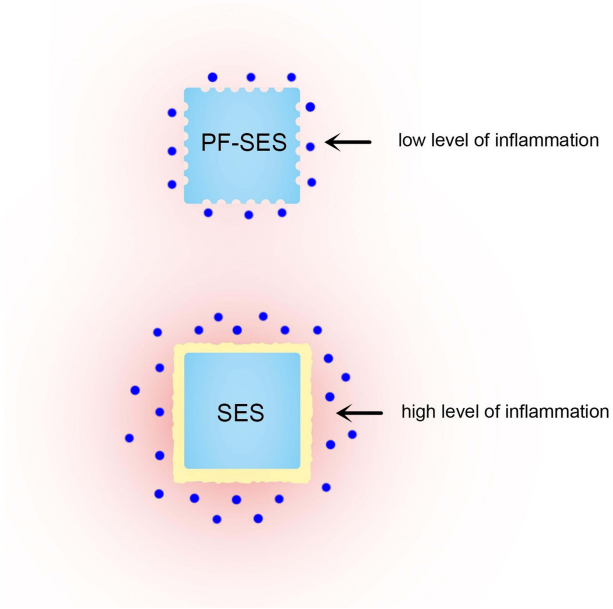


Figure 5 Demonstration of the different drug-eluting mechanisms between PF-SES and SES.

drug release.[24] Stent design, anti-proliferative drug, and the presence and type of polymer are the key factors of a DES platform relate to its clinical efficacy.

Inflammation plays a critical role in the pathological mechanism of neointimal proliferation following stent placement. The polymer used in DES, which helps load and control the release of antiproliferative drugs, has been suspected of contributing to inflammatory responses and delayed arterial healing.[4] The presence of a permanent polymer coating has been identified as a potential trigger for inflammatory reactions, which may contribute to the development of neoatherosclerosis, resulting in ISR and subsequent TVR.[10,25] Polymer-free DESs were initially developed with the hope that eliminating the polymer would reduce the risk of polymer-related inflammation and late thrombotic events.[26]

Prospective studies have demonstrated that CRP, a general marker of systemic inflammation, is associated with an increased risk of diabetes.[27] Studies that have identified an independent association between CRP and diabetes suggest various pathways. Many researchers argue that this association reflects the effects of cytokines, such as IL-6 and tumor necrosis factor (TNF)-α, on insulin resistance.[28,29] The inflammatory process plays a significant role in the development of diabetes. Cross-sectional epidemiological data have shown that elevated serum CRP levels are associated with obesity, insulin resistance, and glucose intolerance.[30] These findings suggest that inflammation impacts blood glucose levels and raises the risk of diabetes through pathways involving obesity or insulin resistance. An accumulating body of evidence indicates that inflammation may play a critical intermediary role in the pathogenesis of diabetes, linking it to numerous commonly coexisting conditions believed to originate through inflammatory mechanisms.[8] The clinical outcomes in our study, which were worse for polymer-coated stents, appear to support the hypothesis that the additional inflammation induced by the polymer, combined with the heightened inflammation associated with diabetes, results in an additive pro-inflammatory effect at the site of vascular reendothelialization following stent implantation.

Stent implantation-induced vascular injury triggers the release of growth factors from endothelial cells, platelets, and macrophages. These growth factors play a crucial role in reendothelialization.[31] The inflammatory response to durable polymer coatings or drugs delays cell coverage during the initial stages of strut coverage, which is the primary mechanism behind stent thrombosis—a major factor leading to adverse cardiac events after coronary stent implantation.[31,32] In our study, no significant difference in serum CRP levels was observed between the PF-SES and SES groups. However, the CRP levels in both groups exceeded the normal range, indicating a state of chronic inflammation in CAD patients with type 2 DM. Serum CRP reflects the overall inflammatory state of the body rather than the local inflammatory level of coronary atherosclerotic lesions. Therefore, we utilized OCT to evaluate both local

tissue structural changes and the local inflammatory level of the intima after stent implantation in coronary atherosclerotic lesions. Indicators such as heterogeneous, lipid layer, intimal tears, thrombi, and micro-vessels were used to reflect these local inflammatory levels.

OCT has emerged as a highly valuable tool for assessing reendothelialization following stent implantation.[33] This intravascular imaging technique provides high-resolution, cross-sectional images of the coronary arteries, allowing for detailed visualization of the stent and the surrounding vascular tissue.[34] Particularly in patients with type 2 diabetes, who are at a higher risk of adverse cardiovascular events, OCT can offer critical insights into the healing process post-stent implantation. By identifying areas of incomplete reendothelialization, neointimal hyperplasia, and potential in-stent restenosis, OCT helps clinicians make informed decisions regarding patient management and follow-up care.[35] Moreover, OCT can differentiate between various tissue components within the vessel wall, such as lipid-laden intima and plaque microstructures, which is essential for a comprehensive assessment of atherosclerosis.[36] This detailed visualization supports the optimization of stent design and the development of new therapeutic strategies aimed at improving long-term outcomes for CAD patients with type 2 DM.

The traditional SES are associated with an inflammatory response due to the durable polymer coatings. This inflammation can delay cell coverage during the initial stages of strut coverage, which is a primary mechanism behind stent thrombosis. Stent thrombosis is a significant factor leading to adverse cardiac events after coronary stent implantation. For patients with type 2 DM, who already have higher baseline levels of inflammation, this additional inflammatory response could potentially worsen clinical outcomes.[37,38] In contrast, the PF-SES, such as the Nano Plus stent, have an improved uniform drug distribution on the abluminal stent surface. This design significantly differs from traditional SES in terms of the drug-eluting mechanism, potentially leading to lower levels of inflammation. For type 2 DM patients, this could mean a reduced risk of inflammation-induced vascular complications. Therefore, for diabetic patients, who are at a heightened risk of inflammation, PF-SES might be a more suitable option. The reduced inflammatory response could help in better vascular reendothelialization and potentially improve long-term clinical outcomes.

Some limitations warrant discussion. Our study is subject to several limitations. First, its retrospective nature may introduce inherent biases and constraints commonly associated with such study designs. However, the current analysis highlights the safety and efficacy of PF-SES in an unselected population in a real-world setting. Second, data were collected solely from one medical center, potentially limiting the generalizability of our findings to broader population characteristics. In terms of patient disease composition, the proportion of STEMI patients in the polymer-free group was notably lower than that in the polymer-coated group. Given the poorer prognosis associated with STEMI patients, this could potentially lead to inferior clinical outcomes in the polymer-coated group. Due to the presence of such selection bias, we plan to conduct a prospective, multicenter, randomized controlled trial in the future.

Conclusions

PF-SES could effectively improve in-stent reendothelialization in patients with type 2 DM, with positive effects on survival rate and may, therefore, be considered as an alternative treatment option for improving clinical long-term outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study protocol, approved by the ethics committees of the First Hospital of Jilin University, adhered to the principles outlined in the Declaration of Helsinki and its subsequent amendments. Prior to participation, all patients were provided with detailed information regarding the study objectives, following which their consent was obtained.

Acknowledgments

The authors thank the study subjects for their participation and support of this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by China postdoctoral science foundation (grant no. 2018M641870 to RZ).

Disclosure

All authors report no conflicts of interest in this work.

References

1. Moses JW, Leon MB, Popma JJ. et al. 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.
2. 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(12):1267–1274. doi:10.1016/j.jcin.2013.06.015.
3. Schwartz RS, Chronos NA, Virmani R. Preclinical restenosis models and drug-eluting stents: still important, still much to learn. *J Am Coll Cardiol*. 2004;44(7):1373–1385. doi:10.1016/j.jacc.2004.04.060.
4. 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.
5. 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(1):193–202. doi:10.1016/j.jacc.2006.03.042.
6. Costa RA, Abizaid A, Mehran R, et al. Polymer-free biolimus A9-coated stents in the treatment of de novo coronary lesions: 4- and 12-month angiographic follow-up and final 5-year clinical outcomes of the prospective, multicenter BioFreedom FIM clinical trial. *JACC Cardiovasc Interv*. 2016;9(1):51–64. doi:10.1016/j.jcin.2015.09.008.
7. Baquet M, Jochheim D, Mehilli J. Polymer-free drug-eluting stents for coronary artery disease. *J Interv Cardiol*. 2018;31(3):330–337. doi:10.1111/joic.12499.
8. Pradhan AD, Manson JE, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286(3):327–334. doi:10.1001/jama.286.3.327.
9. Fröhlich M, Imhof A, Berg G, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. *Diabetes Care*. 2000;23(12):1835–1839. doi:10.2337/diacare.23.12.1835.
10. van Hemert ND, Voskuil M, Rozemeijer R, et al. 3-year clinical outcomes after implantation of permanent-polymer versus polymer-free stent: reCre8 landmark analysis. *JACC Cardiovasc Interv*. 2021;14(22):2477–2486.
11. American Diabetes Association Professional Practice Committee. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S17–S38.
12. Jiang Z, Zhang R, Sun M, et al. Effect of clopidogrel vs ticagrelor on platelet aggregation and inflammation markers after percutaneous coronary intervention for ST-elevation myocardial infarction. *Can J Cardiol*. 2018;34(12):1606–1612. doi:10.1016/j.cjca.2018.08.024.
13. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134(10):e123–55. doi:10.1161/CIR.0000000000000404.
14. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *Circulation*. 2022;145(3):e4–e17.
15. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40(2):87–165. doi:10.1093/eurheartj/ehy394.
16. Liu X, Zhang R, Hou J, et al. Interleukin-35 promotes early endothelialization after stent implantation by regulating macrophage activation. *Clin Sci*. 2019;133(7):869–884. doi:10.1042/CS20180879
17. Prati F, Regar E, Mintz GS, et al. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J*. 2010;31(4):401–415. doi:10.1093/eurheartj/ehp433.

18. Rieber J, Meissner O, Babaryka G, et al. Diagnostic accuracy of optical coherence tomography and intravascular ultrasound for the detection and characterization of atherosclerotic plaque composition in ex-vivo coronary specimens: a comparison with histology. *Coron Artery Dis*. 2006;17(5):425–430. doi:10.1097/00019501-200608000-00005.
19. Kato K, Yonetsu T, Kim SJ, et al. Nonculprit plaques in patients with acute coronary syndromes have more vulnerable features compared with those with non-acute coronary syndromes: a 3-vessel optical coherence tomography study. *Circ Cardiovasc Imaging*. 2012;5(4):433–440. doi:10.1161/CIRCIMAGING.112.973701.
20. Bharadwaj AS, Vengrenyuk Y, Yoshimura T, et al. Multimodality intravascular imaging to evaluate sex differences in plaque morphology in stable CAD. *JACC Cardiovasc Imaging*. 2016;9(4):400–407. doi:10.1016/j.jcmg.2016.02.007.
21. Bukka M, Rednam PJ, Sinha M. Drug-eluting balloon: design, technology and clinical aspects. *Biomed Mater*. 2018;13(3):032001. doi:10.1088/1748-605X/aaa0aa.
22. Wessely R. New drug-eluting stent concepts. *Nat Rev Cardiol*. 2010;7(4):194–203. doi:10.1038/nrcardio.2010.14
23. Mori H, Gupta A, Torii S, et al. Clinical implications of blood-material interaction and drug eluting stent polymers in review. *Expert Rev Med Devices*. 2017;14(9):707–716. doi:10.1080/17434440.2017.1363646.
24. Srdanovic I. Factors Influencing 1st and 2nd generation drug-eluting stent performance: understanding the basic pharmaceutical drug-in-polymer formulation factors contributing to stent thrombosis do we really need to eliminate the polymer? *J Pharm Pharm Sci*. 2021;24:435–461. doi:10.18433/jpps32053.
25. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. *Eur Heart J*. 2015;36(32):2147–2159. doi:10.1093/eurheartj/ehv205.
26. Dai Y, Wang R, Chen F, et al. Clinical outcomes in 2481 unselected real-world patients treated with a polymer-free sirolimus-eluting stent: 3 years results from the NANO multicenter registry. *BMC Cardiovasc Disord*. 2021;21(1):537. doi:10.1186/s12872-021-02356-0.
27. Dehghan A, Kardys I, de Maat MP, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes*. 2007;56(3):872–878. doi:10.2337/db06-0922.
28. Duncan BB, Schmidt MI, Pankow JS, et al. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52(7):1799–1805. doi:10.2337/diabetes.52.7.1799.
29. Hu FB, Meigs JB, Li TY, et al. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53(3):693–700. doi:10.2337/diabetes.53.3.693.
30. Doi Y, Kiyohara Y, Kubo M, et al. Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: the Hisayama study. *Diabetes Care*. 2005;28(10):2497–2500. doi:10.2337/diacare.28.10.2497.
31. Yang X, Thomas DP, Zhang X, et al. Curcumin inhibits platelet-derived growth factor-stimulated vascular smooth muscle cell function and injury-induced neointima formation. *Arterioscler Thromb Vasc Biol*. 2006;26(1):85–90. doi:10.1161/01.ATV.0000191635.00744.b6.
32. Liu X, Zhang R, Fu G, et al. Methotrexate therapy promotes cell coverage and stability in in-Stent Neointima. *Cardiovasc Drugs Ther*. 2021;35(5):915–925. doi:10.1007/s10557-020-07121-7.
33. Jiménez-Valero S, Moreno R, Sánchez-Recalde A. Very late drug-eluting stent thrombosis related to incomplete stent endothelialization: in-vivo demonstration by optical coherence tomography. *J Invasive Cardiol*. 2009;21(9):488–490.
34. Wang TJ, Yang YJ, Xu B, et al. Atorvastatin accelerates both neointimal coverage and re-endothelialization after sirolimus-eluting stent implantation in a porcine model: new findings from optical coherence tomography and pathology. *Circ J*. 2012;76(11):2561–2571. doi:10.1253/circj.CJ-12-0468
35. Hommels TM, Hermanides RS, Fabris E, et al. Exploring new insights in coronary lesion assessment and treatment in patients with diabetes mellitus: the impact of optical coherence tomography. *Cardiovasc Diabetol*. 2023;22(1):123.
36. Iaccarino D, Politi L, Rossi R, et al. Rationale and study design of the OISTER trial: optical coherence tomography evaluation of stent struts re-endothelialization in patients with non-ST-elevation acute coronary syndromes--a comparison of the intrEpide tRapidil eluting stent vs. taxus drug-eluting stent implantation. *J Cardiovasc Med*. 2010;11(7):536–543.
37. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. 2005;365(9467):1333–1346. doi:10.1016/S0140-6736(05)61032-X.
38. Akbari M, Hassan-Zadeh V. The inflammatory effect of epigenetic factors and modifications in type 2 diabetes. *Inflammopharmacology*. 2020;28(2):345–362. doi:10.1007/s10787-019-00663-9.