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Five-year clinical outcomes of the first Korean-made sirolimus-eluting coronary stent with abluminal biodegradable polymer

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Abstract

This study evaluated the 5-year clinical outcomes of the Genoss DES, the first Korean-made sirolimus-eluting coronary stent with abluminal biodegradable polymer.

We previously conducted the first-in-patient prospective, multicenter, randomized trial with a 1:1 ratio of patients using the Genoss DES and Promus Element stents; the angiographic and clinical outcomes of the Genoss DES stent were comparable to those of the Promus Element stent. The primary endpoint was major adverse cardiac events (MACE), which was a composite of death, myocardial infarction (MI), and target lesion revascularization (TLR) at 5 years.

We enrolled 38 patients in the Genoss DES group and 39 in the Promus Element group. Thirty-eight patients (100%) from the Genoss DES group and 38 (97.4%) from the Promus Element group were followed up at 5 years. The rates of MACE (5.3% vs 12.8%, $P = .431$), death (5.3% vs 10.3%, $P = .675$), TLR (2.6% vs 2.6%, $P = 1.000$), and target vessel revascularization (TVR) (7.9% vs 2.6%, $P = .358$) at 5 years did not differ significantly between the groups. No TLR or target vessel revascularization was reported from years 1 to 5 after the index procedure, and no MI or stent thrombosis occurred in either group during 5 years.

The biodegradable polymer Genoss DES and durable polymer Promus Element stents showed comparable low rates of MACE at the 5-year clinical follow-up.

Abbreviations: BP = biodegradable polymers, DAPT = dual antiplatelet therapy, DES = drug-eluting stent; DP = durable polymer, MACE = major adverse cardiac events, MI = myocardial infarction, ST = stent thrombosis, TLF = target lesion failure, TLR = target lesion revascularization, TVR = target vessel revascularization.

Keywords: coronary artery disease, drug-eluting stents, Sirolimus

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K-WS and H-MY equally contributed to this work.

The authors report no conflicts of interest.

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

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1. Introduction

Percutaneous coronary intervention with a drug-eluting stent (DES) is an established standard treatment for flow-limiting coronary artery disease as the rates of restenosis and adverse clinical events associated with these stents are lower than those with bare-metal stents.[1,2] However, there were some safety concerns associated with first-generation DESs, such as late and very late stent thrombosis (ST).[3,4] From the point of view of the stent characteristics, ST could be associated with delayed endothelization caused by the eluting drugs and inflammation or a delayed hypersensitivity reaction due to the polymers.[5–9] Therefore, numerous efforts have been made to improve the stent design including thinner stent struts, a biocompatible or biodegradable polymer coating, and the use of new antiproliferative drugs.[10,11] Compared to the outcomes of the first-generation DESs, the second-generation DESs have shown improved long-term clinical outcomes.[12–16]

The Genoss DES (Genoss Company Limited, Suwon, Korea) is the first sirolimus-eluting cobalt-chromium coronary stent with abluminal biodegradable polymers (BP) made in Korea. The thickness of the Genoss DES stent strut is 70 μm, and the polymers are fully resorbable within 9 months. The Genoss DES stent was found to be noninferior to the Promus Element stent (Boston Scientific, Natick, MA) with respect to late lumen loss at

the 9-month angiography follow-up. Furthermore, the intravascular ultrasound-derived minimal lumen area after stenting during the index procedure and after 9 months were not significantly different between the groups in the first-in-patient prospective randomized study.[17] Furthermore, there were no differences in the clinical outcomes between the 2 groups during the 9 months of follow-up. The aim of this study was to compare the clinical outcomes of patients treated with the BP Genoss DES stent with those of patients treated with the durable polymer (DP) Promus Element stent after a 5-year clinical follow-up.

2. Methods

2.1. Study design

The study design was previously described in the first-in-patient study of Genoss DES.[17] In summary, this study was a prospective, multicenter, randomized trial with a 1:1 ratio of patients using the Genoss DES and Promus Element stents conducted at four Korean centers. The inclusion criteria were patients with stable or unstable angina, silent ischemia, and *de novo* coronary stenotic lesions with a diameter stenosis >50%, reference vessel diameter of 2.5 to 4.0 mm, and maximum lesion length of 40 mm. The exclusion criteria were the evidence of acute myocardial infarction (MI), cardiogenic shock, left ventricular ejection fraction <40%, contraindications to antiplatelet agents, chronic total occlusion lesions, in-stent restenosis, and left main or graft vessel disease. The protocol was approved by the Institutional Review Boards of the Ajou University Hospital, Yonsei University Wonju Christian Hospital, Seoul National University Hospital, and Seoul St. Mary's Hospital, and all patients provided written informed consent.

The patients were randomly allocated treatment with the Genoss DES and Promus Element stents in a 1:1 ratio. Percutaneous coronary intervention was performed according to standard techniques, and there were no restrictions based on the duration of dual antiplatelet therapy after 9 months, number of stents, or number/severity/location of lesions. Patients were followed up through hospital visits at 1, 5, and 9 months after the procedure and yearly up till 5 years. The primary endpoint was major adverse cardiac events (MACE), which was a composite of death, MI, and target lesion revascularization (TLR) at 5 years. The secondary endpoints included death, MI, TLR, target vessel revascularization (TVR), and ST within 5 years.

2.2. Statistical analysis

Categorical variables are presented as frequency (percentage), and continuous variables are presented as mean ± standard deviation. Continuous variables were compared using the unpaired Student *t* test, and categorical variables were compared using the χ^2 or Fisher exact test. Survival curves were constructed using Kaplan–Meier estimates with the log-rank test comparison. All statistical analyses were performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL). A *P* value of <.05 was considered statistically significant.

3. Results

Between March 2013 and April 2015, 80 patients were randomized to the Genoss DES or Promus Element group in a 1:1 ratio. After a total of 3 patients were excluded in both groups (1 patient did not undergo stent implantation, 1 had a protocol violation, and 1 patient withdrew from the study), 38 patients received the Genoss DES stent, and 39 patients received the Promus Element stent. Among them, 38 patients (100%) from the Genoss DES and 38 patients (97.4%) from the Promus Element groups were followed up for 5 years. As previously reported,[17] there were no differences in the baseline clinical, angiographic, and procedural characteristics between the 2 groups (mean age, 64 ± 8 years in the Genoss DES group vs 63 ± 8 years in the Promus Element group, *P* = .591; male, 81.6% vs 79.5%, *P* = 1.000; diabetes, 31.6% vs 30.8%, *P* = 1.000; hypertension, 63.2% vs 74.4%, *P* = .332; clinical diagnosis, *P* = .549; lesion type as per the American Heart Association/American College of Cardiology classification, *P* = .089; mean number of stents, 1.2 vs 1.1, *P* = .099, respectively) (Tables 1 and 2).

There was also no statistically significant difference in the use of dual antiplatelet agents at the 1-, 2-, 3-, 4-, and 5-year follow-ups between the 2 groups (100% in the Genoss DES group vs 100% in the Promus Element group, *P* = 1.000; 36.8% vs 25.6%, *P* = .289; 21.1% vs 20.5%, *P* = .953; 8.8% vs 18.4%, *P* = .240; 8.8% vs 15.8%, *P* = .372, respectively) (Table 3).

At the 5-year follow-up, there were no significant differences in the rates of MACE between the groups (5.3% in the Genoss DES group vs 12.8% in the Promus Element group, *P* = .431) (Table 4). The 2 groups also did not show any significant differences in the rates of death (5.3% vs 10.3%, *P* = .675), MI

Table 1

Baseline clinical characteristics.

	Genoss DES (n = 38)	Promus Element (n = 39)	*P*
Age, y	64 ± 8	63 ± 8	.591
Male	31 (81.6%)	31 (79.5%)	1.000
Diabetes	12 (31.6%)	12 (30.8%)	1.000
Hypertension	24 (63.2%)	29 (74.4%)	.332
Hyperlipidemia	15 (39.5%)	13 (33.3%)	.640
Current smoker	9 (23.7%)	13 (33.3%)	.451
Diagnosis			.549
Stable angina	17 (44.7%)	19 (48.7%)	
Unstable angina	21 (55.3%)	19 (48.7%)	
Silent ischemia	0	1 (2.6%)	

Table 2

Angiographic and procedural characteristics.

	Genoss DES (n = 38)	Promus Element (n = 39)	*P* value
Target vessel			.068
Left anterior descending	18 (47.3%)	26 (66.7%)	
Left circumflex	4 (10.5%)	6 (15.4%)	
Right coronary	16 (42.1%)	7 (17.9%)	
AHA/ACC classification			.089
A	4 (10.5%)	7 (17.9%)	
B1	6 (15.8%)	14 (35.9%)	
B2	10 (26.3%)	8 (20.5%)	
C	18 (47.4%)	10 (25.6%)	
Stent diameter, mm	3.14 ± 0.26	3.15 ± 0.30	.970
Stent length, mm	25.5 ± 8.6	24.1 ± 5.0	.395
Mean stent number	1.2	1.1	.099
Stent overlap	8 (21.1%)	3 (7.7%)	.114

ACC = American College of Cardiology, AHA = American Heart Association.

Table 3

Antiplatelet-agent use.

	Genoss DES (n = 38)	Promus Element (n = 39)	*P*
DAPT			.591
At 1 y	38 (100%)	39 (100%)	.000
At 2 y	14 (36.8%)	10 (25.6%)	.289
At 3 y	8 (21.1%)	8 (20.5%)	.953
At 4 y	3 (8.8%)	7 (18.4%)	.240
At 5 y	3 (8.8%)	6 (15.8%)	.372

DAPT = dual antiplatelet therapy.

(0% vs 0%, $P = 1.000$), TLR (2.6% vs 2.6%, $P = 1.000$), TVR (7.9% vs 2.6%, $P = .358$), and ST (0% vs 0%, $P = 1.000$). Five patients died from noncardiac causes including aggravated renal function, chronic lymphocytic leukemia, cholangiocarcinoma, lung cancer, and prostate cancer. No case of TLR or TVR was reported from years 1 to 5 after the index procedure. Kaplan–Meier curves comparing the clinical endpoints between patients treated with the Genoss DES and Promus Element stents are shown in Figure 1.

Table 4

Clinical outcomes at 9 months and at 5 years.

9 mo	Genoss DES (n = 38)	Promus Element (n = 39)	*P*
Death	1 (2.6%)	0	.494
Cardiac	0	0	
Noncardiac	1 (2.6%)	0	
MI	0	0	1.000
TLR	1 (2.6%)	1 (2.6%)	1.000
TVR	3 (7.9%)	1 (2.6%)	.358
Stent thrombosis	0	0	1.000

5 y	Genoss DES (n = 38)	Promus Element (n = 39)	*P* value
MACE	2 (5.3%)	5 (12.8%)	.431
Death	2 (5.3%)	4 (10.3%)	.675
Cardiac	0	1 (2.6%)	
Noncardiac	2 (5.3%)	3 (7.7%)	
MI	0	0	1.000
TLR	1 (2.6%)	1 (2.6%)	1.000
TVR	3 (7.9%)	1 (2.6%)	.358
Stent thrombosis	0	0	1.000

MACE = major adverse cardiac events, MI = myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

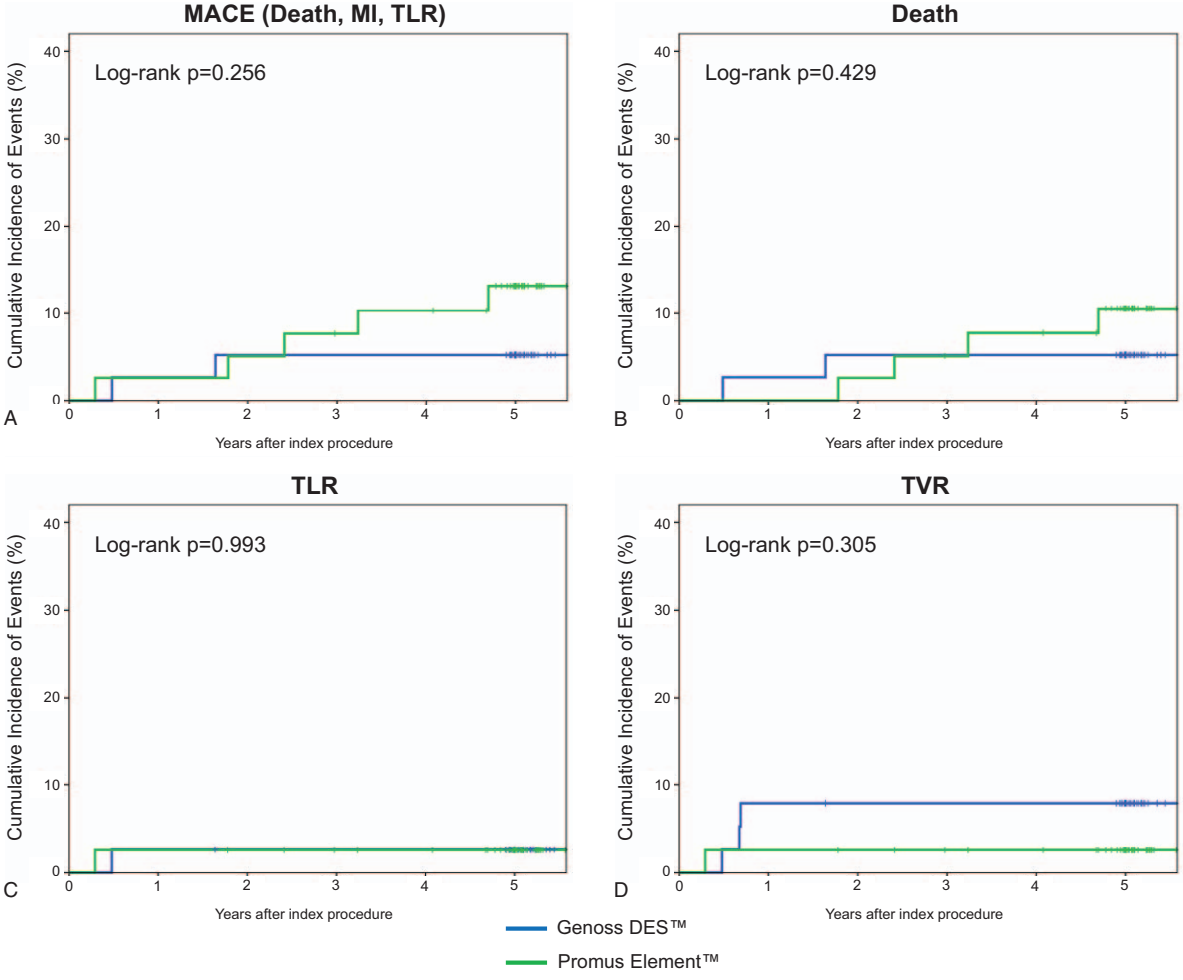

Figure 1. Kaplan–Meier curves for the clinical endpoints comparing patients treated with the Genoss DES and Promus Element stents. (A) MACE; (B) Death; (C) TLR; (D) TVR. DES = drug-eluting stent, MACE = major adverse cardiac events, MI = myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

4. Discussion

This study reported the 5-year clinical outcomes of the Genoss DES in the first-in-patient prospective, multicenter, randomized study. At 5 years, there were no significant differences in the rates of adverse clinical events among patients of the Genoss DES and Promus Element stent groups. Overall, the rates of MACE were very low, and there were no hard endpoints such as MI or ST in either group. Thus, these findings confirm the long-term safety and efficacy of the Genoss DES in the selected patients.

In the previously reported first-in-patient study,[17] the in-stent late lumen loss at the 9-month angiographic follow-up did not differ significantly between the groups (0.11 ± 0.25 mm for Genoss DES vs 0.16 ± 0.43 mm for Promus Element, $P = .567$), and the rates of death, MI, TLR, and TVR at 9 months were also not significantly different.

Recently, a study of an ongoing Genoss DES prospective registry was published.[18] This was a prospective, single-arm, observational, multicenter trial in which 622 consecutive patients were enrolled at 16 centers in South Korea. At 12 months, the rate of the device-oriented composite outcome, defined as cardiac death, target vessel-related MI, and TLR, was 0.6%. It consisted of cardiac death in 1 patient, target vessel MI in 1 patient, and TLR in 3 patients. This study demonstrated the excellent safety and efficacy of the Genoss DES in real-world practice.

Conceptually, the BP-DES was developed to overcome the delayed endothelization, inflammation, or delayed hypersensitivity reaction to the polymer. Therefore, the clinical outcomes using the BP-DES are expected to be better than those using the DP-DES.[5–9] In this study, the rates of adverse events were similar between the 2 groups and lower than those found in other studies comparing the BP-DES and DP-DES. The rates of MACE or target lesion failure (TLF) were comparable between the BP-DES and DP-DES in 5-year follow-up studies as follows: the BIOSCIENCE trial (MACE, 20.2% in BP-DES vs 18.8% in DP-DES, $P = .487$),[19] ISAR-TEST 4 trial (MACE, 28.6% vs 28.4%, $P = .93$),[12] BIOFLOW-II trial (TLF, 10.4% vs 12.7%, $P = .473$),[20] COMPARE II trial (MACE, 22.2% vs 17.2%, $P = .34$),[21] and EVOLVE trial (TLF, 5.5% vs 7.2%, $P = .65$).[22] A recent meta-analysis revealed similar long-term clinical outcomes between the BP-DES and DP-DES groups.[23,24] However, the incidence of definite or probable ST tended to be lower in the BP-DES group than in the DP-DES group (odds ratio, 95% confidence interval; 0.78, 0.59–1.01) during 63 months of follow-up.[23]

During the 5-year follow-up in our study, the absence of ST and MI in both groups was remarkable. At 5 years, 8.8% patients with the Genoss DES stent and 15.8% with the Promus Element stent were on dual antiplatelet therapy (DAPT), the rates of which were similar between the 2 groups. In the BIOSCIENCE study,[19] the definite or probable ST rate and the DAPT rate at the 5-year follow-up was 6.3% and 8%, respectively, in the BP-SES group and 7.7% and 7%, respectively, in the DP-everolimus-eluting stent group. In the EVOLVE trial,[22] there was no ST in either group with a DAPT rate of 16.7% in the permanent polymer DES group and 12.2% in the BP-EES group at the 5-year follow-up.

5. Limitations

This study has some limitations. First, the sample size was too small. Second, due to the nature of the first-in-patient study, most of the enrolled patients had simple or uncomplicated lesions.

6. Future directions

In future, a clinical follow-up consisting of a large study population in a real-world setting is needed.

7. Conclusion

The BP Genoss DES and DP Promus Element stents showed comparable low rates of MACE at the 5-year clinical follow-up.

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