



# Long-Term Clinical Outcomes of Drug-Coated Balloon Treatment for De Novo Coronary Lesions

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**Purpose:** Data are limited on the long-term efficacy and safety of drug-coated balloon (DCB) treatment in comparison to drug-eluting stent (DES) for de novo coronary lesions. We investigated the long-term clinical outcomes of DCB treatment in percutaneous coronary intervention (PCI) for de novo coronary lesions.

**Materials and Methods:** A total of 103 patients scheduled for elective PCI for de novo non-small coronary lesions ( $\geq 2.5$  mm) who were successfully treated with DCB alone were retrospectively compared with 103 propensity-matched patients treated with second-generation DES from the PTRG-DES registry ( $n=13160$ ). All patients were followed for 5 years. The primary endpoint was major adverse cardiac events [MACE; cardiac death, myocardial infarction, stroke, target lesion thrombosis, target vessel revascularization (TVR), and major bleeding] at 5 years.

**Results:** At 5-year clinical follow-up, Kaplan-Meier estimates of the rate of MACE were significantly lower in the DCB group [2.9% vs. 10.7%; hazard ratio (HR): 0.26; 95% confidence interval (CI): 0.07–0.96; log-rank  $p=0.027$ ]. There was a significantly lower incidence of TVR in the DCB group (1.0% vs. 7.8%; HR: 0.12; 95% CI: 0.01–0.98; long-rank  $p=0.015$ ), and there was major bleeding only in the DES group (0.0% vs. 1.9%; log-rank  $p=0.156$ ).

**Conclusion:** At 5-year follow-up, DCB treatment was significantly associated with reduced incidences of MACE and TVR, compared with DES implantation, for de novo coronary lesions.

**Key Words:** Balloon, drug-eluting stent, long-term effects, major adverse cardiac events

## INTRODUCTION

Although drug-eluting stent (DES) implantation holds impor-

tant positions in the percutaneous coronary intervention (PCI) era for coronary artery disease (CAD), late stent thrombosis and restenosis, at an annual incidence of nearly 2%, remains an unsolved issue.<sup>1,2</sup> Drug-coated balloon (DCB) treatment without a vascular cage, such as a stent, is an attractive therapeutic option and may have several advantages over stent-based strategies in various CAD settings.<sup>3</sup> DCB treatment currently has an established indication in the treatment of in-stent restenosis lesions and de novo small vessel disease, as well as patients presenting with high bleeding risk.<sup>4-7</sup>

For de novo small vessel disease, previous trials have reported similar rates of major adverse cardiac events (MACE) for up to 3 years in patients treated with DCB or second-generation DES implantation.<sup>5,8,9</sup> Jeger, et al.<sup>5</sup> reported MACE rates of 15%

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in DCB and DES groups [hazard ratio (HR): 0.99; 95% confidence interval (CI): 0.68–1.45;  $p=0.95$ ]. However, these studies were limited to de novo small coronary vessel and up to 3 years of follow-up. Recent observational studies have indicated that the efficacy and safety of DCB treatment are comparable for de novo non-small coronary lesions and small vessel disease.<sup>10,11</sup> Her, et al.<sup>10</sup> demonstrated that target vessel failure (TVF) rates were similar between groups at 3.4 years of follow-up (large vessel group, 7.0% vs. small vessel group, 7.9%;  $p=0.596$ ). Another recent meta-analysis indicated that DCB treatment was non-inferior to DES implantation for de novo large coronary lesions in terms of target lesion revascularization at 6–9 months of follow-up [risk ratio (RR):1.17; 95% CI: 0.46–2.95;  $p=0.746$ ].<sup>12</sup> However, there is a paucity of data of the long-term (>3 years) efficacy and safety of DCB treatment in comparison to DES implantation for de novo coronary lesions.

Therefore, this study aimed to investigate the long-term clinical outcomes of DCB treatment, compared with second-generation DES implantation, for de novo coronary lesions at 5 years of follow-up.

## MATERIALS AND METHODS

### Study population

A total of 103 patients treated successfully with PCI for de novo CAD using a DCB-only strategy were retrospectively enrolled from Ulsan University Hospital in South Korea (Impact of Drug-coated Balloon Treatment in de Novo Coronary Lesion; NCT04619277) between April 2011 and December 2013. Patients with significant de novo major epicardial CAD ( $\geq 50\%$  diameter stenosis on angiography) with documented ischemia on a treadmill test or fractional flow reserve (FFR) who were scheduled to undergo PCI were considered eligible for this study. The angiographic inclusion criteria were the presence of a de novo non-small coronary lesion with a reference vessel diameter  $\geq 2.5$  mm and a Thrombolysis In Myocardial Infarction (TIMI) flow of 3 following balloon angioplasty. Exclusion criteria were severe left ventricular dysfunction (ejection fraction  $<35\%$ ), chronic kidney disease, ST-segment elevation myocardial infarction requiring primary PCI, significant left main CAD, ostial or heavily calcified or thrombotic lesions, a life expectancy of  $<1$  year, and loss to follow-up. The results were compared with those of 103 propensity-matched patients treated with DES implantation from the Platelet function and genotype-Related long-term prognosis in Drug-Eluting Stent-treated Patients with coronary artery disease (PTRG-DES) consortium (<https://www.clinicaltrials.gov>) (unique identifier: NCT04734028). This consortium consists of nine prospective registries from 32 Korean academic centers, with data covering 13160 patients who underwent DES implantation between July 2003 and August 2018.<sup>13</sup> Among the 13160 PTRG-DES consortium patients, 11226 were treated with sec-

ond-generation DES, and 9566 patients received DES implantation in that same period like the DCB cohort. Propensity score matching (PSM) was performed for 1947 of them who had been followed up for 5 years. The data supporting the findings of this study are available from the corresponding author upon reasonable request. The corresponding author had full access to all data in this study and takes responsibility for data integrity and data analyses. The study protocol was approved by the Institutional Review Board of Ulsan University Hospital, and the study was conducted in accordance with the 2013 Declaration of Helsinki (NCT04619277).

### Procedure

All patients were pretreated with aspirin 200 mg and clopidogrel 300 or 600 mg as loading doses, followed by intravenous injection of unfractionated heparin 100 U/kg to maintain an activated clotting time of  $\geq 250$  s during the procedure. Intracoronary nitroglycerin (200  $\mu$ g) was administered before the diagnostic coronary angiography. For the DCB treatment group, pre-dilation with a plain balloon was mandatory (using the recommended balloon-to-vessel ratio of 0.8 to 1.0). After pre-dilation balloon angioplasty, DCB treatment was considered in cases without severe dissection (A to C), provided TIMI flow grade 3 was present. The DCB was inflated to its nominal pressure for at least 60 s, with care taken to extend the DCB at least 2 mm beyond the initial pre-dilation. Each DCB was coated with 3.0  $\mu$ g/mm<sup>2</sup> paclitaxel combined with iopromide (Se-Quent Please® by B. Braun, Melsungen, Germany) as a carrier for the drug. After DCB application, the final assessment was performed at least 5 min after the administration of a bolus of an intracoronary vasodilator to catch any remaining acute vessel closure. In cases of high thrombus burden, a bailout glycoprotein IIb/IIIa receptor inhibitor strategy was used. The duration of the prescribed dual antiplatelet therapy (DAPT) was determined at the discretion of the attending physician.

### End points and follow-up

After the index PCI, all 206 patients underwent clinical follow-up for 5 years. Meticulous clinical follow-up with telephone interviews and outpatient clinic visits revealed the clinical outcomes. The primary endpoint was MACE, defined as the composite of cardiac death, myocardial infarction (MI), stroke, probable or definite target lesion thrombosis, target vessel revascularization (TVR), and major bleeding, at 5 years. Cardiac death was defined as any death that was not clearly of extracardiac origin, including MI, according to guidelines.<sup>14,15</sup> Probable or definite target lesion thrombosis was defined according to the Academic Research Consortium definition,<sup>16</sup> and TVR was defined as any repeat PCI of any segment in the target vessel. Major bleeding was defined as Bleeding Academic Research Consortium type 3–5 bleeding.<sup>17</sup>

## Statistical analysis

For continuous variables, intergroup differences were evaluated using the unpaired t-test or Mann-Whitney rank test. Data are expressed as means±standard deviation. For discrete variables, intergroup differences are expressed as counts and percentages, and were analyzed with the  $\chi^2$  or Fisher's exact test. In the intergroup comparison of clinical outcomes, the cumulative incidences of MACE and other outcomes were estimated using the Kaplan-Meier method, and the curves were compared using the log-rank test. To reduce the effect of potential confounding factors in an observational study, we used PSM to adjust for differences in baseline characteristics. The propensity score was estimated using logistic regression by considering demographic and clinical variables (age, sex, body mass index, hypertension, diabetes, current smoking, end-stage renal disease, previous history of MI, previous history of PCI, left main disease, multivessel disease, presentation of acute MI, chronic total occlusion, total number of treated vessels). Patients were 1:1 matched using the nearest-neighbor method with respect to the calculated score. All *p* values were two-sided, and values of <0.05 were considered statistically significant. R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform the statistical analyses.

## RESULTS

The baseline clinical and procedural characteristics of the patients are described in Table 1. The mean patient age was 58.3 years in the DCB group and 58.2 years in the DES group, and the majority of them were male. The baseline clinical and procedural characteristics in both groups were well balanced after PSM adjustment, except for the prevalence of left circumflex artery disease [DCB group: 50 (48.5%) vs. DES group: 26 (25.2%); *p*=0.001]. Although the number of treated vessels was the same, the total number of devices used (DCB group: 1.1±0.2 vs. DES group: 1.3±0.5; *p*<0.001), total device length (DCB group: 24.2±6.3 mm vs. DES group: 29.1±14.7 mm; *p*=0.002), and mean device diameter (DCB group: 2.7±0.4 mm vs. DES group: 3.1±0.4 mm; *p*<0.001) were different. In the DCB group, there was no bail-out stenting.

Table 2 and Fig. 1 highlight comparisons of the cumulative incidences of major clinical outcomes between the DCB and DES groups for the 5-year follow-up. The cumulative incidence of MACE was significantly lower in the DCB group [3 (2.9%)] than in the DES group [11 (10.7%)] (HR: 0.26; 95% CI: 0.07–0.96; log-rank *p*=0.027). Kaplan-Meier survival curves (Fig. 2) showed superior event-free survival up to 5 years in the DCB group, compared with the DES group. There was a significantly lower incidence of TVR in the DCB group [1 (1.0%) vs. 8 (7.8%); HR: 0.12; 95% CI: 0.01–0.98; long-rank *p*=0.015], and major bleeding was only recorded in the DES group [0 (0.0%) vs. 2 (1.9%); log-rank *p*=0.156]. The cumulative incidences of

**Table 1.** Baseline Clinical and Procedural Characteristics

|                                    | DCB treatment<br>(n=103) | DES treatment<br>(n=103) | <i>p</i><br>value |
|------------------------------------|--------------------------|--------------------------|-------------------|
| Clinical characteristics           |                          |                          |                   |
| Age, yr                            | 58.3±9.9                 | 58.2±10.4                | 0.945             |
| Sex, male                          | 75 (72.8)                | 72 (69.9)                | 0.758             |
| Body mass index, kg/m <sup>2</sup> | 24.2±2.9                 | 24.1±2.8                 | 0.792             |
| Hypertension                       | 59 (57.3)                | 51 (49.5)                | 0.328             |
| Diabetes mellitus                  | 36 (35.0)                | 36 (35.0)                | >0.999            |
| Current smoker                     | 60 (58.3)                | 56 (54.4)                | 0.673             |
| Prior MI                           | 13 (12.6)                | 12 (11.7)                | >0.999            |
| Prior PCI                          | 28 (27.2)                | 27 (26.2)                | >0.999            |
| End-stage renal disease            | 5 (4.9)                  | 3 (2.9)                  | 0.718             |
| Clinical presentation              |                          |                          |                   |
| Stable angina                      | 40 (38.8)                | 52 (50.5)                | 0.123             |
| Unstable angina                    | 46 (44.7)                | 33 (32.0)                | 0.086             |
| Acute MI                           | 18 (17.5)                | 18 (17.5)                | >0.999            |
| Procedural characteristics         |                          |                          |                   |
| Target lesion                      |                          |                          |                   |
| Left main                          | 2 (1.9)                  | 0                        | 0.477             |
| LAD                                | 62 (60.2)                | 52 (50.5)                | 0.207             |
| LCX                                | 50 (48.5)                | 26 (25.2)                | 0.001             |
| RCA                                | 34 (33.0)                | 26 (25.2)                | 0.283             |
| Multivessel disease                | 35 (34.0)                | 33 (32.0)                | 0.882             |
| Chronic total occlusion            | 6 (5.8)                  | 8 (7.8)                  | 0.782             |
| Total number of diseased vessel    | 1.4±0.7                  | 1.4±0.7                  | >0.999            |
| Total number of treated vessel     | 1.0±0.2                  | 1.0±0.1                  | 0.315             |
| Total number of device used        | 1.1±0.2                  | 1.3±0.5                  | <0.001            |
| Total device length, mm            | 24.2±6.3                 | 29.1±14.7                | 0.002             |
| Mean device diameter, mm           | 2.7±0.4                  | 3.1±0.4                  | <0.001            |
| Medication at discharge            |                          |                          |                   |
| DAPT                               | 101 (98.1)               | 98 (95.1)                | 0.442             |
| Statin                             | 96 (94.1)                | 88 (85.4)                | 0.069             |
| Calcium channel blocker            | 33 (32.7)                | 14 (13.6)                | 0.002             |
| Beta blocker                       | 27 (26.5)                | 60 (58.3)                | <0.001            |

DCB, drug-coated balloon; DES, drug-eluting stent; MI, myocardial infarction; PCI, percutaneous coronary intervention; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DAPT, dual antiplatelet therapy.

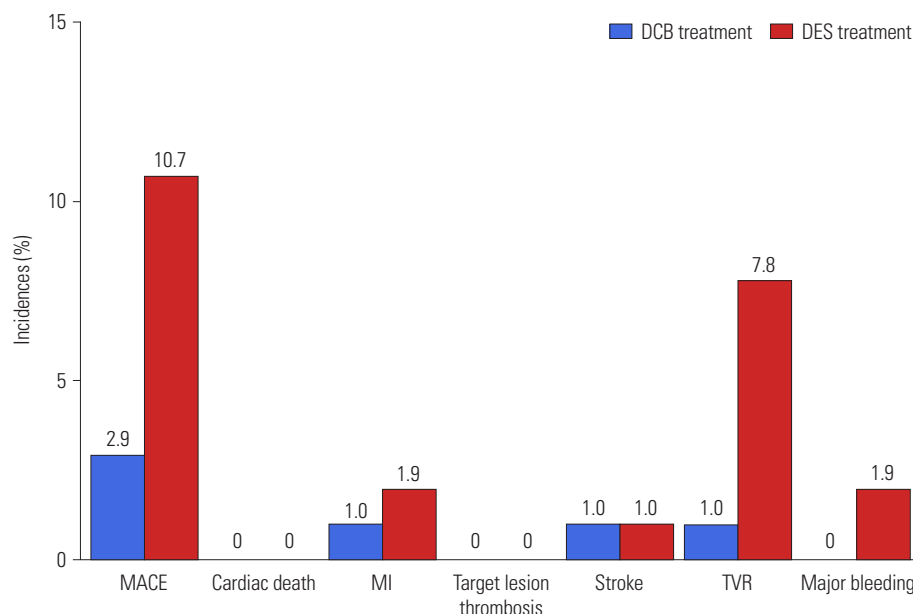
Data are presented as n (%) or mean±standard deviation.

**Table 2.** Clinical Outcomes after 5 Years of Follow-Up in DCB Group and DES Group

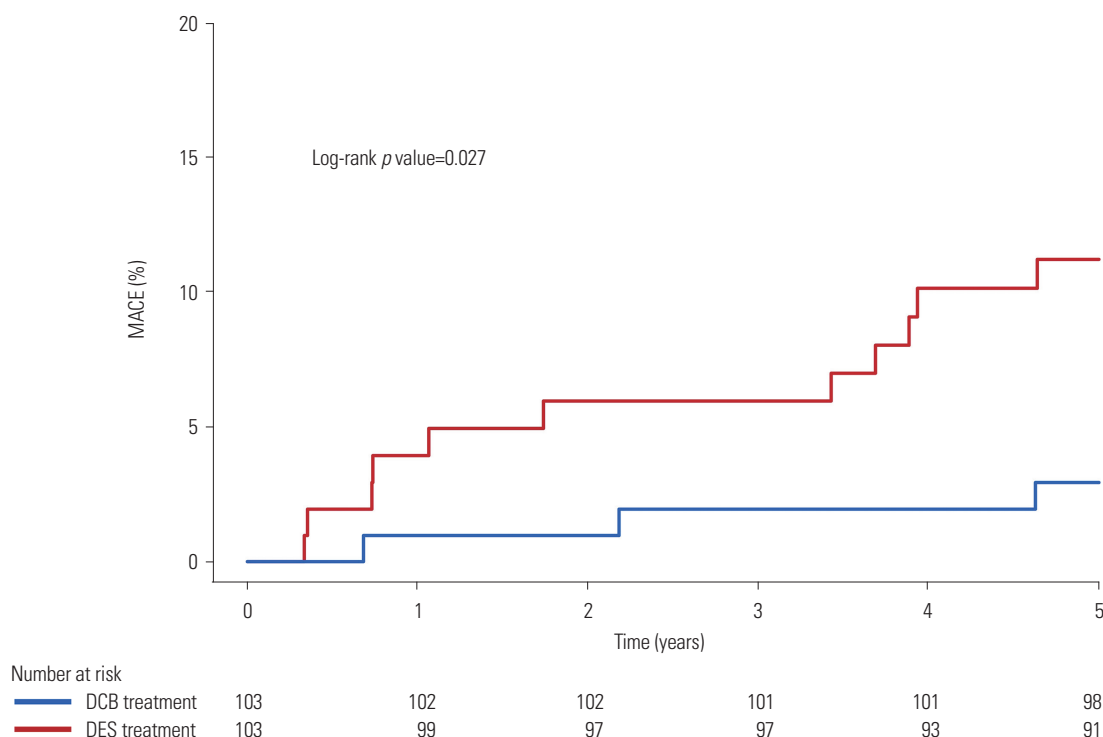
| Outcomes                 | DCB treatment<br>(n=103) | DES treatment<br>(n=103) | <i>p</i> value |
|--------------------------|--------------------------|--------------------------|----------------|
| MACE                     | 3 (2.9)                  | 11 (10.7)                | 0.027          |
| Cardiac death            | 0                        | 0                        | -              |
| MI                       | 1 (1.0)                  | 2 (1.9)                  | 0.558          |
| Stroke                   | 1 (1.0)                  | 1 (1.0)                  | 0.997          |
| Target lesion thrombosis | 0                        | 0                        | -              |
| TVR                      | 1 (1.0)                  | 8 (7.8)                  | 0.015          |
| Major bleeding           | 0                        | 2 (1.9)                  | 0.156          |

DCB, drug-coated balloon; DES, drug-eluting stent; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization.

Data are presented as n (%).



**Fig. 1.** Comparison of major clinical outcomes after 5 years of follow-up in the DCB group and DES group. DCB, drug-coated balloon; DES, drug-eluting stent; MACE, major adverse cardiac events; MI, myocardial infarction; TVR, target vessel revascularization.



**Fig. 2.** Kaplan-Meier curve for freedom from MACE during 5 years of follow-up for the DCB group and DES group. DCB, drug-coated balloon; DES, drug-eluting stent; MACE, major adverse cardiac events.

MI and stroke did not significantly differ between groups [MI: DCB group: 1 (1.0%) vs. DES group: 2 (1.9%); HR: 0.50; 95% CI: 0.04-5.46; log-rank  $p=0.558$ ; stroke: DCB group: 1 (1.0%) vs. DES group: 1 (1.0%); HR: 1.00; 95% CI: 0.06-15.91; log-rank  $p=0.997$ ]. There were no cases of cardiac death or target lesion thrombosis in either group.

## DISCUSSION

The main finding of this study is that DCB treatment showed excellent long-term 5-year clinical outcomes in terms of MACE and TVR, compared with DES implantation, for de novo coronary lesions and appeared to be safe and effective for 5 years of follow-up.

The advantages of DCB treatment include homogeneous drug delivery to the vessel wall, immediate drug release without the use of a polymer, the potential for reducing antiplatelet therapy intensity and duration, and the freedom of leaving no foreign object behind in the vessel.<sup>18</sup> PCI with DES remains an unresolved issue because the predisposition for increases in stent thrombosis and restenosis limits the safety and efficacy of DES.<sup>2</sup> Previous studies have suggested that a thicker stent strut design and durable polymers might drive TVF and late stent thrombosis.<sup>1,19</sup> Therefore, DCB treatment may reduce intimal hyperplasia and vessel inflammation in the absence of metallic stent struts and polymer, thereby permitting short-term DAPT and the preservation of vessel anatomy and flow, compared with DES.<sup>20</sup>

Currently, the available evidence of the long-term efficacy and safety of DCB treatment, compared with DES implantation, in de novo coronary lesions is limited to small vessel disease and 1–3 years after PCI.<sup>5,8,9</sup> These trials have shown that similar rates of MACE occurred in both groups, along with numerically higher incidences of MI and vessel thrombosis, in the DES group. However, the safety and efficacy of DCB treatment beyond 3 years for de novo coronary lesions remain unestablished, and previous studies of de novo non-small coronary lesions have reported conflicting results limited by the absence of a control group treated with DES implantation.<sup>11,21,22</sup>

Our study results were consistent with those of previous studies on the long-term clinical outcomes in de novo non-small coronary lesions. We showed that DCB treatment was significantly associated with lower rates of MACE than DES implantation [DCB group: 3 (2.9%) vs. DES group: 11 (10.7%); HR: 0.26; 95% CI: 0.07–0.96; log-rank  $p=0.027$ ] and TVR [DCB group: 1 (1.0%) vs. DES group: 8 (7.8%); HR: 0.12; 95% CI: 0.01–0.98; log-rank  $p=0.015$ ]. Scheller, et al.<sup>21</sup> demonstrated that the rates of all-cause mortality and cardiac death for coronary intervention with DCB were significantly reduced, compared to those of other device groups, after 3 years of follow-up (all-cause mortality: RR: 0.73; 95% CI: 0.53–1.00;  $p=0.047$ ; cardiac death: RR: 0.53; 95% CI: 0.33–0.85;  $p=0.009$ ). However, this analysis had some limitations in terms of its relatively short-term follow-up period ( $\leq 3$  years) and inclusion of significantly heterogeneous control groups, such as plain old balloon angioplasty, use of bare metal stents, and various in-stent restenosis settings. Merinopoulos, et al.<sup>22</sup> showed that paclitaxel DCB was not associated with increased late mortality for up to 5 years of follow-up and reported a trend toward better survival versus non-paclitaxel second-generation DES ( $p=0.083$ ). However, this non-matched analyzed study showed only all-cause mortality as long-term clinical outcomes; included only patients with stable disease, excluding those with acute coronary syndrome; and included a relatively short follow-up period (median follow-up: 31.6 months for DCB vs. 44.4 months for DES), compared with our study (inclusion of patients with unstable angina and non-ST-elevation MI; follow-up of 60 months).

Therefore, our study may be meaningful in that we directly compared the long-term safety and efficacy of DCB treatment for de novo non-small coronary lesions with second-generation DES for up to 5 years.

Our study identified a significantly lower incidence of TVR in the DCB group [1 (1.0%) vs. 8 (7.8%); HR: 0.12; 95% CI: 0.01–0.98; long-rank  $p=0.015$ ], and there were only two major bleedings in the DES group [0 (0.0%) vs. 2 (1.9%); log-rank  $p=0.156$ ] at 5 years of follow-up. These findings were consistent with those of earlier studies.<sup>12,23,24</sup> A recent meta-analysis of DCB treatment versus other device strategies showed that the former was associated with lower target lesion revascularization rates than bare metal stents (RR: 0.19; 95% CI: 0.04–1.00) and similar target lesion revascularization rates as DES (RR: 1.37; 95% CI: 0.62–3.05) ( $P_{\text{interaction}}=0.03$ ) at 12 months of follow-up.<sup>23</sup> Previous studies have suggested that mechanical impairment of the vessel wall with thicker stent strut and localized inflammation around metal struts with durable polymers might drive late stent thrombosis and TVF.<sup>1,9</sup> In contrast, DCB has the advantage of locally delivering the antiproliferative drug without the need for metal struts, thereby directly inhibiting the process of neointimal hyperplasia and negative remodeling. Additionally, several studies have described positive remodeling, vascular healing, and plaque regression after DCB treatment, confirming the advantages of DCB with intravascular ultrasound (IVUS) and optical coherence tomography (OCT).<sup>25,26</sup> Another possible explanation for the lower TVR rate in the DCB group may be related to differences in the use of FFR or intravascular imaging, such as IVUS and OCT, which may have affected the overall outcomes. Although the frequency of using FFR or intravascular imaging in the DES group is unknown, it is noteworthy that a relatively high proportion of patients in the DCB group utilized FFR [75 (72.8%)], IVUS [80 (77.7%)], or OCT [25 (24.3%)]. Furthermore, even with propensity matching, it is possible that differences in device number and length between both groups may have also played a role. Overall, the lower TVR rate in the DCB group is likely due to a combination of several factors, and further research is needed to better understand these factors and how they impact outcomes. In addition, for major bleeding events, the recent sub-group analysis of the BASKET SMALL 2 trial suggested that rates of major bleeding events tended to be lower in the DCB group than in the DES group, even among high bleeding risk patients, at 3 years of follow-up (1.6% vs. 3.7%,  $p=0.064$ );<sup>27</sup> this finding was consistent with that of our study. Our results also support DCB treatment as an attractive alternative to DES implantation for patients who cannot tolerate prolonged DAPT.

This study has several limitations. First, it has an innate limitation regarding its single-center registry, observational nature, and small study population that did not target all types of coronary lesions. Therefore, our results cannot be generalized to patients beyond the study inclusion criteria and protocol. However, we tried to overcome this limitation by applying PSM

adjustments to minimize bias from different baseline characteristics. Second, the study population came from an expert center with a DCB-only strategy for treating de novo CAD. Thus, these results may not be applicable to other patient populations without an adequate learning curve. Third, we could not obtain precise data on medication, including DAPT, during the follow-up period of our study. Although both groups adhered to the standard antiplatelet therapy guidelines based on the physician's assessment, there is a possibility that variation in DAPT during the follow-up period between the two groups could influence the results. Finally, our data were compared with data from the PTRG-DES registry, which did not include angiographic outcomes, such as quantitative coronary analysis and intravascular imaging analysis. Therefore, further randomized clinical trials with large numbers of patients are necessary to evaluate the long-term efficacy and safety of DCB treatment versus DES implantation, including both clinical and angiographic outcomes for de novo coronary lesions.

In conclusion, in the treatment of de novo coronary lesions, DCB treatment showed excellent 5-year clinical outcomes in terms of MACE and TVR, compared with DES implantation. This study will help bolster evidence of the long-term safety and efficacy of DCB treatment for de novo coronary lesions.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Ae-Young Her and Eun-Seok Shin. **Data curation:** Ae-Young Her and Bitna Kim. **Formal analysis:** Ae-Young Her and Bitna Kim. **Funding acquisition:** Young-Hoon Jeong and Eun-Seok Shin. **Investigation:** Ae-Young Her, Soe Hee Ahn, Yongwhi Park, Jung Rae Cho, Young-Hoon Jeong, and Eun-Seok Shin. **Methodology:** Ae-Young Her and Eun-Seok Shin. **Project administration:** Yongwhi Park and Jung Rae Cho. **Resources:** Young-Hoon Jeong and Eun-Seok Shin. **Software:** Soe Hee Ahn and Yongwhi Park. **Supervision:** Eun-Seok Shin. **Validation:** Jung Rae Cho and Young-Hoon Jeong. **Visualization:** Ae-Young Her, Bitna Kim, and Eun-Seok Shin. **Writing—original draft:** Ae-Young Her. **Writing—review & editing:** Ae-Young Her and Eun-Seok Shin. **Approval of final manuscript:** all authors.

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