

NEW RESEARCH PAPER

CORONARY

Clinical Impact of Drug-Coated Balloon-Based Percutaneous Coronary Intervention in Patients With Multivessel Coronary Artery Disease



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ABSTRACT

BACKGROUND Data on drug-coated balloon (DCB) treatment in the context of multivessel coronary artery disease (CAD) are limited.

OBJECTIVES The purpose of this study was to investigate the impact of DCB-based treatment on percutaneous coronary intervention for multivessel CAD.

METHODS A total of 254 patients with multivessel disease successfully treated with DCBs or in combination with drug-eluting stents (DES) were retrospectively enrolled (DCB-based group) and compared with 254 propensity-matched patients treated with second-generation DES from the PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) registry (n = 13,160) (DES-only group). Major adverse cardiovascular events (MACE) comprised cardiac death, myocardial infarction, stroke, stent thrombosis, target vessel revascularization, and major bleeding at 2 years.

RESULTS Baseline clinical characteristics were comparable between the groups. In the DCB-based group, 34.3% of patients were treated with DCBs only and 65.7% were treated with the DES hybrid approach. The number of stents and total stent length were significantly reduced by 65.4% and 63.7%, respectively, in the DCB-based group compared with the DES-only group. Moreover, the DCB-based group had a lower rate of MACE than the DES-only group (3.9% and 11.0%; $P = 0.002$) at 2-year follow-up. The DES-only group had a higher risk for cardiac death and major bleeding.

CONCLUSIONS The DCB-based treatment approach showed a significantly reduced stent burden for multivessel percutaneous coronary intervention and led to a lower rate of MACE than the DES-only treatment. This study shows that DCB-based treatment approach safely reduces stent burden in multivessel CAD, and improved long-term outcomes may be expected by reducing stent-related events. (Impact of Drug-Coated Balloon Treatment in De Novo Coronary Lesion; [NCT04619277](#)) (J Am Coll Cardiol Intv 2023;16:292-299) © 2023 by the American College of Cardiology Foundation.

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The length and number of stents are known to independently predict in-stent restenosis and thrombosis,^{1–3} even in the era of second-generation drug-eluting stents (DES).⁴ Furthermore, stent implantation may impair restoration of vasomotion in stented segments and accelerate neoatherosclerosis.^{5,6} Recently, the Grand-DES (Korean Nationwide Multicenter Pooled Registry of Drug-Eluting Stents) registry demonstrated that multivessel disease, multiple stenting, and long stent length were significant predictors of ischemic clinical events in patients undergoing percutaneous coronary intervention (PCI).³ In previous studies, drug-coated balloon (DCB) treatment has been associated with noninferior clinical outcomes compared with DES implantation in patients with in-stent restenosis⁷ and de novo small-vessel disease.^{8,9} As it does not leave any of the lesion behind, the DCB strategy reduces the risk for stent-associated maladaptive biologic response, which is responsible for restenosis and thrombosis; this promotes vessel healing.^{6,10} The International Consensus Group¹¹ and Asian Pacific Consensus Group¹² reported that a DCB-only approach in native lesions is feasible and may safely replace DES if revascularization using predilation balloon angioplasty is achieved with favorable results. However, using DCB or in combination with DES as part of a hybrid procedure to reduce stent burden (stent length or number) may be an alternative and useful treatment approach for multivessel disease. Here, we report the data and clinical outcomes of patients who underwent treatment with DCB or in combination with DES for multivessel coronary artery disease (CAD). We then compared these findings with those of propensity-matched patients who were treated with DES only from the PTRG-DES (Platelet Function and Genotype-Related Long-Term Prognosis in Drug-Eluting Stent-Treated Patients With Coronary Artery Disease) consortium (NCT04734028).

METHODS

PATIENT POPULATION. A total of 254 patients with successful PCI for multivessel CAD using DCBs or in combination with the DES hybrid approach were retrospectively enrolled from 3 teaching hospitals in South Korea (Ulsan University Hospital, Ulsan Medical Center, and Korea University Ansan Hospital) with experience in treating patients with multivessel CAD using DCBs (Impact of Drug-Coated Balloon Treatment in De Novo Coronary Lesion; NCT04619277). Eligible patients were those who had lesions $\geq 50\%$ narrowed and whom the investigator considered to require PCI for ≥ 2 major epicardial coronary lesions.

Patients were excluded from the analysis if they had previously undergone coronary artery bypass surgery; presented with cardiogenic shock, thrombolysis before PCI, single-vessel disease, or suboptimal or failed PCI for target lesions; or were lost to follow-up. Additionally, patients' vessels were required to be sufficiently large to accommodate DES. The results of the hybrid approach in these patients were compared with those among 254 propensity-matched patients from the PTRG-DES consortium, who were treated with DES only. This consortium combined 9 prospective registries from 32 Korean academic centers, contributing data from 13,160 patients with DES treated between July 2003 and August 2018.¹³ Among a total of 13,160 PTRG-DES consortium patients, 11,226 patients received second-generation DES, and among them, 4,460 patients underwent multivessel DES implantation. Propensity score matching was performed for 4,427 patients, excluding 33 patients who had previously undergone coronary artery bypass graft. The study protocol was approved by the Institutional Review Board of each participating center, and all patients provided written informed consent at the time of enrollment.

PROCEDURE. All patients were pretreated with aspirin 200 mg and clopidogrel 300 or 600 mg as loading doses, followed by intravenous injection of 100 U/kg unfractionated heparin to maintain an activated clotting time of ≥ 250 seconds during the procedure. Intracoronary nitroglycerin (200 μ g) was administered before diagnostic coronary angiography was performed. For patients with multivessel disease, PCI target lesions were first determined, and then balloon angioplasty was performed to determine whether DCB treatment would be possible. For the DCB-based treatment group, the intervention was performed according to international and Asia-Pacific consensus recommendations for DCB treatment.^{11,12} Specifically, predilation with a plain balloon was mandatory (using the recommended balloon-to-vessel ratio of 0.8–1.0). After predilation balloon angioplasty, stenting was deferred in all types of dissections (A to E), provided there was TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. In cases of flow-limiting dissection after predilation (TIMI flow grade <3) and $>30\%$ visual residual stenosis, PCI with stent insertion was recommended without the use of a DCB. As an exception, even if flow was normal (ie, TIMI flow grade 3) and the residual diameter stenosis was $\leq 30\%$, the operator could choose to implant a DES or a DCB if the patient

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

DCB = drug-coated balloon

DES = drug-eluting stent(s)

MACE = major adverse cardiovascular event(s)

PCB = paclitaxel-coated balloon

PCI = percutaneous coronary intervention

TABLE 1 Patient Clinical and Procedural Characteristics

	DCB-Based Treatment (n = 254)	DES-Only Treatment (n = 254)	P Value
Age, y	63.0 ± 10.1	64.0 ± 10.9	0.279
Men	186 (73.2)	169 (66.5)	0.122
Hypertension	181 (71.3)	190 (74.8)	0.424
Diabetes mellitus	104 (40.9)	115 (45.3)	0.370
Current smoker	87 (34.3)	82 (32.3)	0.706
Prior MI	25 (9.8)	31 (12.2)	0.479
Prior PCI	38 (15.0)	40 (15.7)	0.902
End-stage renal disease	12 (4.7)	16 (6.3)	0.560
Clinical presentation			
Stable angina	72 (28.3)	97 (38.2)	0.024
Unstable angina	111 (43.7)	82 (32.3)	0.010
Acute myocardial infarction	71 (28.0)	75 (29.5)	0.769
DCB-only treatment	87 (34.3)	0	
Target lesion and procedure characteristics			
Left main	32 (12.6)	40 (15.7)	0.373
Chronic total occlusion	52 (20.5)	48 (18.9)	0.738
Total number of diseased vessels	2.4 (0.5)	2.4 (0.5)	0.727
Total number of treated vessels	2.2 (0.4)	2.2 (0.5)	0.253
Total number of devices used (mean)	2.6 ± 0.9	2.6 ± 0.9	0.627
Total number of devices used (median)	2.0 (2.0-3.0)	2.0 (2.0-3.0)	0.830
Total device length, mm (mean)	65.2 ± 25.4	64.2 ± 30.1	0.673
Total device length, mm (median)	58.5 (47.0-80.0)	59.0 (42.0-84.0)	0.390
Device diameter, mm (mean)	2.8 ± 0.3	2.8 ± 0.4	0.711
Device diameter, mm (median)	2.8 (2.6-3.0)	2.8 (2.5-3.0)	0.141
Total number of DCBs used (mean)	1.7 ± 0.8	0	
Total number of DCBs used (median)	1.0 (1.0-2.0)	0	
Total DCB length, mm (mean)	42.0 ± 23.7	0	
Total DCB length, mm (median)	30.0 (26.0-56.0)	0	
DCB diameter, mm (mean)	2.6 ± 0.3	0	
DCB diameter, mm (median)	2.5 (2.5-2.7)	0	
Small DCB used (diameter ≤2.5 mm)	160/254 (36.0)	0	
Total number of DES used (mean)	0.9 ± 0.8	2.6 ± 0.9	<0.001
Total number of DES used (median)	1.0 (0.0-1.0)	2.0 (2.0-3.0)	<0.001
Total DES length, mm (mean)	23.3 ± 23.1	64.2 ± 30.1	<0.001
Total DES length, mm (median)	22.0 (0.0-35.0)	59.0 (42.0-84.0)	<0.001
DES diameter, mm (mean)	3.2 ± 0.5	2.8 ± 0.4	<0.001
DES diameter, mm (median)	3.2 (3.0-3.5)	2.8 (2.5-3.0)	<0.001
Small DES used (≤2.5 mm)	13/167 (7.8)	109/254 (42.9)	<0.001

Values are mean ± SD, n (%), median (IQR), or n/N (%).

DCB = drug-coated balloon; DES = drug-eluting stent(s); MI = myocardial infarction; PCI = percutaneous coronary intervention.

reported new-onset chest pain after balloon angioplasty or if a change in the ST segment or progression of dissection was noted. The DCB was inflated to its nominal pressure for at least 60 seconds, taking care to extend the DCB at least 2 mm beyond the predilatation balloon length. All DCBs were coated with 3.0 µg/mm² paclitaxel combined with iopromide (SeQuent Please, B. Braun), as a carrier for the drug. After DCB use, the final assessment was performed at least 5 minutes after administering a bolus of an intracoronary vasodilator, to prevent 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 was at the discretion of the attending physician.

CLINICAL FOLLOW-UP AND ENDPOINTS. All 508 patients underwent clinical follow-up following the index procedure via telephone interviews and outpatient clinic visits. The study endpoint was cumulative major adverse cardiovascular events (MACE), a composite of cardiac death, myocardial infarction, stroke, probable or definite stent thrombosis, target vessel revascularization, and major bleeding, at 2 years. Cardiac death was defined as any death that was not clearly of extracardiac origin, including myocardial infarction, according to previously published guidelines.⁶ Additionally, probable or definite stent thrombosis was defined according to the Academic Research Consortium definition,¹⁴ and major bleeding was defined as Bleeding Academic Research Consortium types 3 to 5 bleeding.¹⁵

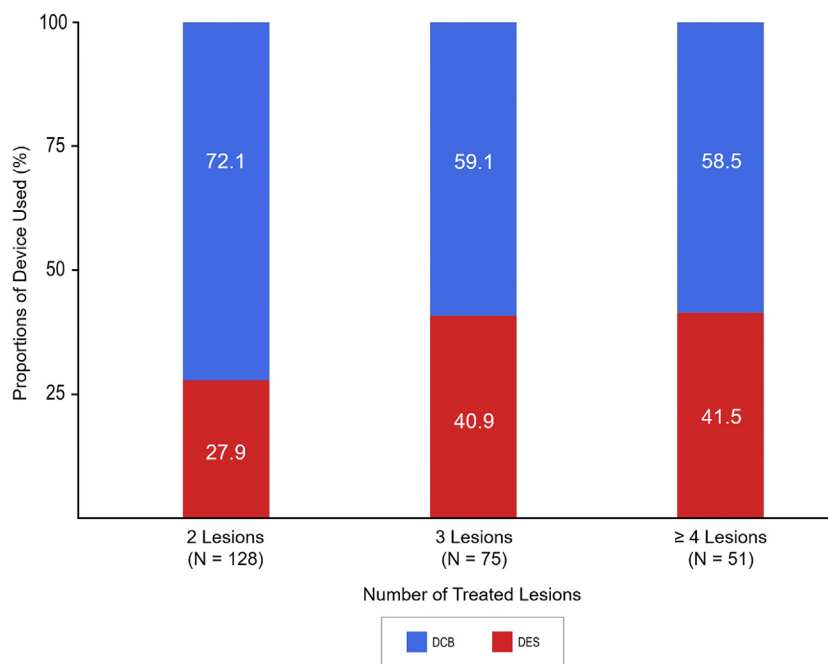
STATISTICAL ANALYSIS. Clinical characteristics are reported as percentages for categorical variables and mean ± SD for continuous variables. Comparisons between groups were made using either the Pearson chi-square test or the Fisher exact test for categorical variables, and Student's *t*-test for continuous variables, as appropriate. In the comparison of clinical outcomes between groups, 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, we used propensity score matching to adjust for differences in baseline characteristics. The propensity score was estimated using logistic regression by considering demographic and clinical variables (sex, age, previous PCI, previous myocardial infarction, diabetes, hypertension, current smoking, end-stage renal disease, left main disease, chronic total occlusion, total number of treated vessels, total number of devices used, mean diameter of device used, and total length of device used). Without setting the caliper size (in R, default caliper size = null), patients were 1:1 matched using the nearest neighbor method with respect to the calculated score. All *P* values were 2-sided, and a value of <0.05 was considered to indicate statistical significance. R version 4.1.2 (R Foundation for Statistical Computing) was used for all statistical analyses in this study.

RESULTS

The baseline clinical and procedural characteristics of the patients are summarized in **Table 1**. The mean age

FIGURE 1 Comparison of Proportions of Device Used According to the Number of Lesions in the DCB-Based Treatment Group



DCB = drug-coated balloon; DES = drug-eluting stent(s).

of the patients was 63.5 years, and the majority of patients were men. Regarding clinical presentation, stable angina was more prevalent in the DES-only group, and unstable angina was more prevalent in the DCB-based group. In the DCB-based group, 34.3% of patients were treated with DCBs alone, and 65.7% were treated with the hybrid approach using DES. The hybrid approach was used for the same vessel in 18.1% of patients (9.0% of vessels). In the DCB-based group, bailout stenting was performed in 2 patients (0.4% of vessels). The prevalence rates of left main disease and chronic total occlusion lesions were comparable between the 2 groups. The total numbers of treated vessels and total numbers of devices used were also comparable between the 2 groups (Table 1). There was a statistically significant difference in the numbers of DCBs and DES used in both groups. In the DCB-based group, the total number of devices used was 2.6 ± 0.9 , of which the number of DCBs was 1.7 ± 0.8 and that of DES was 0.9 ± 0.8 . The total number of DES used in the DES-only group was the same as that in the DCB-based group (2.6 ± 0.9). The mean device diameters were comparable in both groups; the total device length was also similar, at 65.2 ± 25.4 mm in the DCB-based group and 64.2 ± 30.1 mm in the DES-only group. In the DCB-based group, the total

DCB length was 42.0 ± 23.7 mm, and the mean DCB diameter was 2.6 ± 0.3 mm. In the DCB-based group, a small DCB with a diameter of ≤ 2.5 mm was used in 36.0% of patients. The total lengths and mean diameters of the DES used in the 2 groups were significantly different. The total DES length was 23.3 ± 23.1 mm in the DCB-based group and 64.2 ± 30.1 mm in the DES-only group ($P < 0.001$). The mean DES diameter was 3.2 ± 0.5 mm in the DCB-based group and 2.8 ± 0.4 mm in the DES-only group ($P < 0.001$). There was a significant difference between the 2 groups when the mean DES diameter was ≤ 2.5 mm (7.8% in the DCB-based group vs 42.9% in the DES-only group; $P < 0.001$). The number of stents and the total stent length were significantly reduced by 65.4% and 63.7%, respectively, in the DCB-based group compared with those in the DES-only group. Although the number of treated lesions increased, more than one-half of the lesions could be treated with DCBs alone (Figure 1).

CLINICAL OUTCOMES. A comparison of clinical outcomes between the DCB-based (median duration of follow-up 853.0 days; IQR: 530.0-1,344.0 days) and DES-only (median duration of follow-up 804.4 days; IQR: 375.2-1,990.0 days) treatment groups is

TABLE 2 Comparison of Clinical Outcomes Between the 2 Groups at 2-Year Follow-Up

	DCB-Based Treatment (n = 254)	DES-Only Treatment (n = 254)	P Value ^a
Major adverse cardiovascular events ^b	10 (3.9)	28 (11.0)	0.002
Cardiac death	1 (0.4)	6 (2.4)	0.047
Myocardial infarction	0	3 (1.2)	0.082
Stroke	0	1 (0.4)	0.313
Stent thrombosis (definite/probable)	0	1 (0.4)	0.333
Target vessel revascularization	8 (3.1)	16 (6.3)	0.095
Major bleeding	1 (0.4)	7 (2.8)	0.027

Values are n (%). ^aP values were obtained using the log-rank test. ^bMajor adverse cardiovascular events comprised cardiac death, myocardial infarction, stroke, stent thrombosis, target vessel revascularization, and major bleeding (Bleeding Academic Research Consortium bleeding type 3 or greater).
Abbreviations as in Table 1.

presented in **Table 2** and **Central Illustration E**. The DCB-based group had a lower risk for MACE than the DES-only group (3.9% vs 11.0%; $P = 0.002$) at 2-year follow-up. Cardiac death was higher in the DES-only group (0.4% vs 2.4%; $P = 0.047$), and major bleeding was more prevalent in the DES-only group (0.4% vs; 2.8%; $P = 0.027$). No myocardial infarction, stroke, or stent thrombosis was observed in the DCB-based treatment group.

DISCUSSION

The main finding of the present study was that the DCB-based treatment approach for multivessel disease, either alone or in combination with DES, significantly reduced stent burden. It was also associated with a low risk for MACE compared with that of the DES-only approach at 2-year follow-up. Thus, DCB-based treatment is an acceptable approach for the treatment of multivessel CAD.

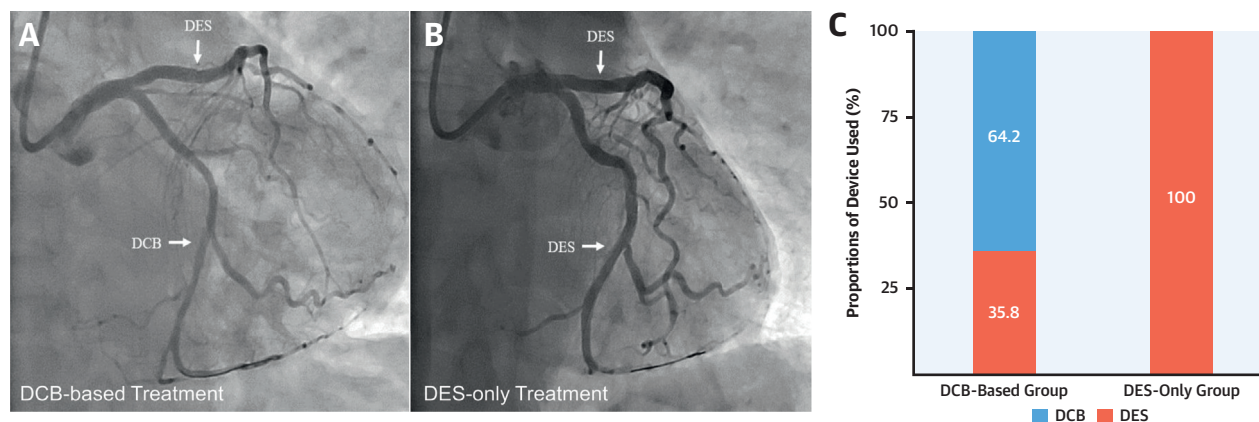
Although outcomes of PCI have improved significantly with the use of new-generation DES, the risk for stent-related adverse events, including cardiac death and myocardial infarction, remains. This risk persists after the acute stage of PCI without plateauing, in contrast to the risk associated with de novo coronary lesions.^{6,16} In a recent study, very late stent-related ischemic events following PCI continued to accrue, even with contemporary DES, at a rate of about 2% per year, with no evident plateau within a 5-year follow-up period.¹⁶ This study demonstrates that an ongoing risk for very late events is common to all types of metallic stents. Several mechanisms have been proposed to explain the ongoing risk for target lesion-related restenosis and stent thrombosis that

are common to all stent platforms. Stent under-expansion and malposition, uncovered struts, hypersensitivity reactions, device fracture, and neoatherosclerosis have all been reported in patients experiencing very late adverse events with metallic coronary stents.¹⁷ Although the development of devices, procedural techniques, and medication regimens for preventing very late events is necessary to further improve lifelong outcomes in patients undergoing coronary revascularization, a treatment method that leaves nothing of the lesions behind will also be useful for improving long-term outcomes.

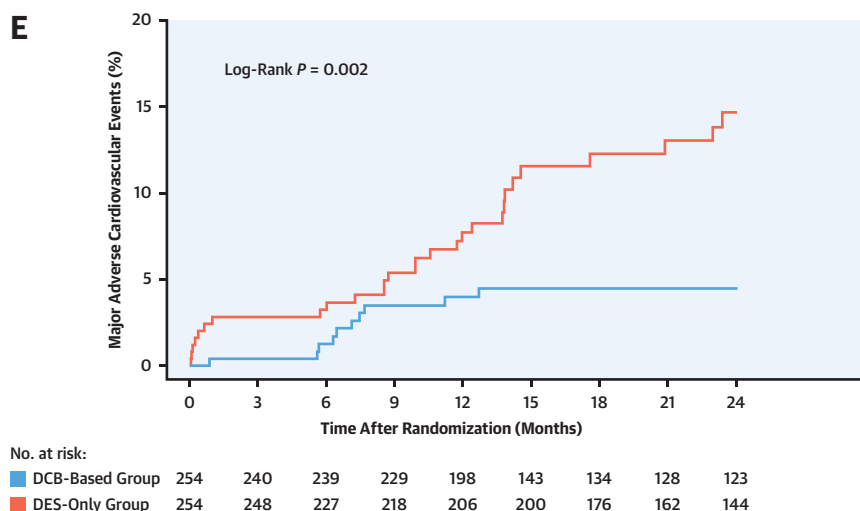
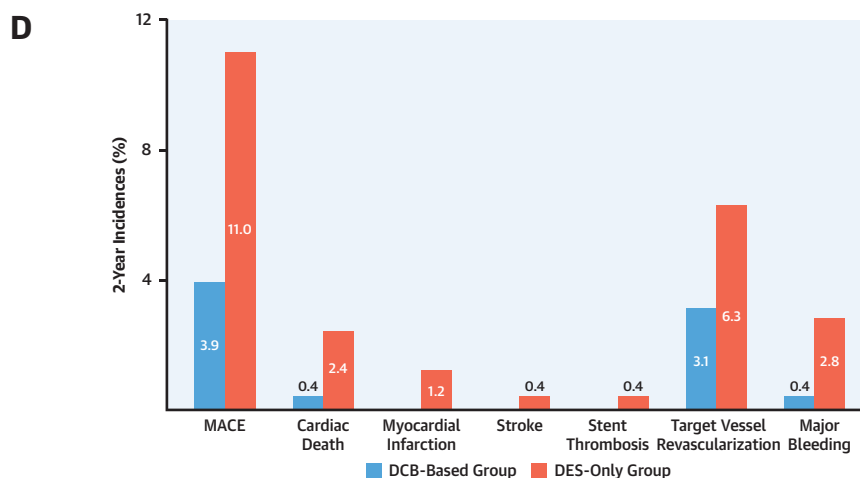
A DCB is a novel concept for the treatment of CAD and an established therapeutic option for in-stent restenosis and small-vessel disease.^{7-9,18} In the BASKET-SMALL 2 (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions) trial, DCBs were non-inferior to DES for lesions of small native coronary arteries with respect to MACE for up to 3 years, with similar event rates for both treatment groups.⁹ Although all-cause death was very similar between the DCB and DES groups (both Kaplan-Meier estimates 8%; HR: 1.05; 95% CI: 0.62-1.77; $P = 0.87$), probable or definite stent thrombosis (Kaplan-Meier estimate 1% vs 2%; HR: 0.33; 95% CI: 0.07-1.64; $P = 0.18$) and major bleeding (Kaplan-Meier estimate 2% vs 4%; HR: 0.43; 95% CI: 0.17-1.13; $P = 0.08$) were numerically lower in the DCB group than in the DES group.⁹ The present study showed better outcomes in the DCB-based treatment group than in the DES-only treatment group in terms of MACE, cardiac death, and major bleeding. Myocardial infarction and stent thrombosis occurred in the DES-only group alone; however, the difference was not significant. These results showed that there was no difference in MACE between the 2 groups until 1 year, but there was a significant difference at 2-year follow-up. Notably, the DCB-based group showed a plateau phenomenon of MACE after 1 year (**Central Illustration E**). Therefore, long-term outcomes may eventually be improved because the DCB-based approach treats lesions without leaving foreign bodies, such as metal stents, even with second-generation DES.

In the Grand-DES registry of patients in whom second-generation DES were used, the combination of 3-vessel disease, total stent length ≥ 60 mm, and ≥ 3 implanted stents continues to be associated with less favorable clinical outcomes with respect to major adverse cardiac and cerebrovascular events at 3 years following PCI.³ In the present study, a hybrid approach using both DCB and DES was used in patients with multivessel disease, and this approach was used for approximately two-thirds of the vessels

CENTRAL ILLUSTRATION Clinical Impact of DCB-Based Percutaneous Coronary Intervention in Patients With Multivessel CAD



2-Year Follow-Up of DCB-Based Versus DES-Only Treatment in 508 Patients With Multivessel CAD



Shin E-S, *et al*. J Am Coll Cardiol Interv. 2023;16(3):292-299.

(A) Representative case from the drug-coated balloon (DCB)-based treatment group. (B) Representative case from the drug-eluting stent (DES)-only treatment group. (C) Comparison of proportions of devices used between the 2 groups. (D) Comparison of clinical outcomes between the 2 groups at 2-year follow-up. (E) Kaplan-Meier curves with cumulative hazards of major adverse cardiovascular events. CAD = coronary artery disease; MACE = major adverse cardiovascular event(s).

treated. In these cases, DES was used in the larger, more proximal lesion sites and DCB was used in the smaller, more distal coronary lesions. The advantages of this hybrid approach include the reduction of overall stent burden (fewer stents or shorter stent length), especially in small vessels and vessels with stents; having a predictor of stent thrombosis, in-stent restenosis, and target lesion revascularization; and treatment of the underlying disease while maintaining access for a future coronary artery bypass graft, if required. A decrease in metal stent length may also preserve vessel response to vasomotion stimuli and reduce the risk for neoatherosclerosis.¹⁹

Our results suggest that DCB use can be an alternative approach to DES for the treatment of multivessel CAD, either alone for smaller coronary vessels or in combination with DES for large proximal lesions. DCB use is also an attractive option for solo use in patients who cannot tolerate prolonged dual antiplatelet therapy. Further studies are required for comprehensive evaluation of the role of DCB treatment in this setting.

STUDY LIMITATIONS. First, this study had an innate limitation regarding its observational nature and the use of registry data. In addition, leaving the choice of treatment strategy to the discretion of the physician inevitably introduces the limitation of selection bias. We addressed this issue by applying extensive sensitivity analyses in which measured or unmeasured confounders were adjusted to minimize the bias from different baseline characteristics.

Second, the study population came from an expert center in DCB-only treatment for de novo CAD. Thus, these results may not be reproducible without an adequate learning curve.

Third, differences between the enrollment periods of the 2 groups might have led to differences in results. Although the PTRG-DES registry has been registered since 2003, the patients whose data were used in the propensity match analysis were cases of second-generation DES. Therefore, differences due to device development and PCI technique improvement are not expected to be significant between the 2 groups. Further prospective randomized noninferiority or superiority clinical trials with larger numbers of patients are needed to evaluate long-term outcomes after DCB-based treatment in multivessel PCI.

CONCLUSIONS

The DCB-based treatment approach showed a significantly reduced stent burden in multivessel PCI, which led to a decrease in MACE at 2 years post-procedure. The findings of this study concretize existing evidence that using DCBs safely reduces stent burden in multivessel CAD, and improved long-term outcomes may be expected by reducing stent-related events. The role of DCB in this setting should be assessed in prospective randomized controlled trials.

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The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? DCBs are an alternative to stents used in selected patients for the treatment of in-stent restenosis lesions and small-vessel disease. However, studies assessing the role of DCBs in multivessel PCI are lacking.

WHAT IS NEW? The DCB-based treatment approach significantly reduced stent burden in multivessel PCI, which led to a reduction in MACE at 2 years. This study showed that the DCB-based approach may safely reduce stent burden in multivessel CAD, and reducing stent-related events is expected to improve long-term outcomes.

WHAT IS NEXT? Further prospective randomized noninferiority or superiority clinical trials with larger numbers of patients are required to evaluate long-term outcomes after DCB-based treatment in multivessel PCI.

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