

Original Research



Clinical Results of Drug-Coated Balloon Treatment in a Large-Scale Multicenter Korean Registry Study

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AUTHOR'S SUMMARY

Current percutaneous coronary intervention has significant limitations related to the implanted current metallic stent. The “leave nothing behind” strategy of drug-coated

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

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balloon (DCB) treatment has showed potential performance to overcome current treatment. However, studies in this issue are still limited by moderate numbers of patients. Therefore, we performed Stent Failure Research DCB registry study to evaluate the efficacy and safety of DCB treatment for in-stent restenosis or de novo lesions. The registry finally included 2,509 patients treated with DCB and revealed the favorable clinical outcome of DCB treatment.

ABSTRACT

Background and Objectives: The aim of this study was to demonstrate the efficacy and safety of treatment with drug-coated balloon (DCB) in a large real-world population.

Methods: Patients treated with DCBs were included in a multicenter observational registry that enrolled patients from 18 hospitals in Korea between January 2009 and December 2017. The primary outcome was target lesion failure (TLF) defined as a composite of cardiovascular death, target vessel myocardial infarction, and clinically indicated target lesion revascularization at 12 months.

Results: The study included 2,509 patients with 2,666 DCB-treated coronary artery lesions (1,688 [63.3%] with in-stent restenosis [ISR] lesions vs. 978 [36.7%] with de novo lesions). The mean age with standard deviation was 65.7±11.3 years; 65.7% of the patients were men. At 12 months, the primary outcome, TLF, occurred in 179 (6.7%), 151 (8.9%), 28 (2.9%) patients among the total, ISR, and de novo lesion populations, respectively. A history of hypertension, diabetes, acute coronary syndrome, previous coronary artery bypass graft, reduced left ventricular ejection fraction, B2C lesion and ISR lesion were independent predictors of 12 months TLF in the overall study population.

Conclusions: This large multicenter DCB registry study revealed the favorable clinical outcome of DCB treatment in real-world practice in patient with ISR lesion as well as small de novo coronary lesion.

Keywords: Coronary stenosis; Angioplasties, coronary balloon

INTRODUCTION

Drug-eluting stent (DES) implantation has been a mainstay in treatment of coronary stenosis worldwide owing to its safety and efficacy.¹⁾ However, restenosis, stent thrombosis, neoatherosclerosis, and abnormal vasomotion remain significant limitations related to the implanted metallic stent that contribute to device-associated cardiovascular events.¹⁻³⁾

Drug-coated balloon (DCB) treatment was initially introduced as a novel therapeutic strategy to overcome in-stent restenosis (ISR).⁴⁻⁶⁾ This treatment is based on the rapid delivery of highly lipophilic drugs to the inner vascular surface after balloon dilation with a unique delivery matrix.⁷⁾ Proper lesion preparation is essential to overcome the limitations of the balloon angioplasty, for example elastic recoils and flow-limiting dissections.⁸⁾ The 2018 European guidelines on myocardial revascularization recommended DCB treatment in patients with bare metal stent (BMS) or DES ISR lesions (class I, evidence level A).⁹⁾ An all-comers, prospective, multicenter registry revealed the safety of DCB treatment and low event rates.¹⁰⁾ The feasibility of the technique in patients with small-vessel coronary artery disease has been suggested in several pilot studies and randomized trials because the “leave nothing behind” strategy of DCB treatment showed no further reduction of the lumen by metallic

DI; Data curation: Cho YK, Kim SW, Koo BK, Bae JW, Lee SH, Yang TH, Park HS, Choi SW, Kim SJ, Jeong YH, Lee HJ, Lee KY, Kim U, Hur SH; Formal analysis: Lee SY, Shin ES; Funding acquisition: Kim SJ; Investigation: Cho YK, Hong YJ, Lee SH, Park HS, Lee HJ; Methodology: Shin ES; Project administration: Hur SH; Resources: Kim SW, Hong YJ, Kim SJ; Supervision: Koo BK, Bae JW, Lee SH, Yang TH, Choi SW, Lim DS, Kim SJ, Jeong YH, Lee KY, Shin ES, Kim MH, Nam CW, Hur SH, Kim DI; Validation: Lee SY, Cho YK, Kim SW, Hong YJ, Bae JW, Lee SH, Park HS, Choi SW, Kim SJ, Lee HJ, Lee KY, Kim U; Writing – original draft: Lee SY, Cho YK; Writing – review & editing: Lee SY, Cho YK, Koo BK, Yang TH, Kim SJ, Lee HJ, Shin ES, Hur SH, Kim DI.

struts.¹⁴) The Third Report of the International DCB Consensus Group has documented that a DCB-only approach in de novo lesions of coronary small-vessel disease is now a valid treatment alternative to DES if current recommendations regarding optimal balloon angioplasty and subsequent DCB delivery are adequately followed.¹⁵ However, studies on the efficacy and safety of DCB treatment in patients with de novo coronary arterial lesions are still limited by moderate numbers of patients. Therefore, we performed this Korean Stent Failure Research (SFR) group DCB registry study to evaluate the efficacy and safety of DCB treatment for ISR or de novo lesions in real-world practice.

METHODS

Ethical statement

The study protocol was approved by the Ethics Committee at each participating center and was conducted according to the principles of the Declaration of Helsinki 2013.

Study population

The SFR DCB registry is a multicenter observational retrospective registry that enrolled patients with percutaneous coronary interventions (PCIs) with DCB treatment from 18 hospitals in Korea between January 2009 and December 2017. Structured medical record review was done to assess clinical events at 12 months.

Procedure

PCIs were performed according to current clinical practice standards. DCB treatment was performed with paclitaxel-eluting balloons (SeQuent Please; B. Braun, Melsungen, Germany and Pantera Lux, Biotronik, Berlin, Germany). Coronary stenotic lesions (ISR or de novo lesions) were predilated with compliant, noncompliant, scoring, or cutting balloons. DCBs were delivered and inflated for 30 to 60 seconds with a nominal pressure. Procedural success was defined as achievement of <30% diameter stenosis without dissection or coronary perforation. Final decision concerning dual antiplatelet treatment duration, type of P2Y₁₂ receptor inhibitors, and use of glycoprotein IIb/IIIa inhibitors was left to the physician's discretion.

Outcomes

The primary outcome was target lesion failure (TLF) at 1 year. TLF was defined as a composite of cardiac death (CD), target vessel myocardial infarction (TVMI), or clinically indicated target lesion revascularization (TLR). Secondary outcomes were each component of TLF. Deaths were considered CD unless a noncardiac cause could be documented. Myocardial infarction was defined according to the Academic Research Consortium definition.¹⁶

An independent clinical event adjudication committee, composed of physicians who were not involved in this study, identified and adjudicated the defined clinical events in a blinded, unbiased manner.

Statistical analysis

Categorical variables were presented as numbers and relative frequencies (percentages) and were compared using the χ^2 test. Continuous variables were expressed as mean \pm standard deviation and were compared using the independent-sample t test or Mann–Whitney test, as appropriate. Calculations of cumulative event rates were based on Kaplan–Meier estimates. A multivariable Cox proportional hazards model was used with backward elimination based

on Akaike information criterion to identify independent predictors of TLF. All p values were 2-sided, with statistical significance set at <0.05. All analyses were conducted using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

All patients

From January 2009 to December 2017, 2,509 patients with 2,666 DCB-treated coronary artery lesions were included. The mean age was 65.7±11.3 years, 69.9% of the patients were men, 43.1% had diabetes, 66.0% had hypertension, and 17.9% were active smokers. Mean left ventricular ejection fraction (LVEF) was 57.5±10.8%. The indication for PCI was an acute coronary syndrome (ACS) in 1,566 patients (62.4%) (Table 1).

Table 1. Baseline patient characteristics

Characteristics	Overall (n=2,509)	De novo (n=964)	ISR (n=1,545)
Demographics			
Female (%)	755 (30.1)	297 (30.8)	458 (29.6)
Age (years)	65.7±11.3	63.9±11.7	66.8±11.0
Current smoking (%)	450 (17.9)	239 (24.8)	211 (13.7)
Hypertension (%)	1,655 (66.0)	595 (61.7)	1,060 (68.6)
Diabetes mellitus (%)	1,082 (43.1)	340 (35.3)	742 (48.0)
Dyslipidemia (%)	1,134 (45.2)	362 (37.6)	772 (50.0)
Dialysis (%)	133 (5.3)	20 (2.1)	113 (7.3)
Previous MI (%)	622 (24.8)	119 (12.3)	503 (32.6)
Previous CABG (%)	48 (1.9)	8 (0.8)	40 (2.6)
Previous CVA (%)	199 (7.9)	74 (7.7)	125 (8.1)
Familial history of premature CAD (%)	202 (8.1)	66 (6.8)	136 (8.8)
Clinical presentation (%)			
Silent ischemia	181 (7.2)	63 (6.5)	118 (7.6)
SA	755 (30.1)	244 (25.3)	511 (33.1)
UA	943 (37.6)	346 (35.9)	597 (38.6)
NSTEMI	502 (20.0)	238 (24.7)	264 (17.1)
STEMI	128 (5.1)	73 (7.6)	55 (3.6)
ACS (%)	1,566 (62.4)	650 (67.4)	916 (59.3)
Laboratory profiles			
EF	57.5±10.8	57.9±10.3	57.3±11.0
LVEF <50% (%)	516 (20.6)	175 (18.2)	341 (22.1)
eGFR	79.5±32.7	85.3±30.5	75.9±33.5
eGFR <60 mL/min/1.73 m ² (%)	541 (21.6)	145 (15.0)	396 (25.6)
Creatinine	1.3±1.6	1.2±1.3	1.5±1.8
Total cholesterol (mg/dL)	151.3±41.5	165.2±43.3	142.6±37.9
HDL cholesterol (mg/dL)	43.2±11.7	44.2±12.0	42.6±11.6
Triglycerides (mg/dL)	132.1±88.9	137.1±97.5	129.0±83.0
LDL cholesterol (mg/dL)	90.4±44.0	102.2±52.7	83.0±35.6
Medication at discharge			
Aspirin (%)	2,405 (95.9)	901 (93.5)	1,504 (97.3)
Clopidogrel (%)	2,079 (82.9)	715 (74.2)	1,364 (88.3)
Ticagrelor (%)	235 (9.4)	148 (15.4)	87 (5.6)
Prasugrel (%)	89 (3.5)	43 (4.5)	46 (3.0)
P2Y12 inhibitor	2,376 (94.7)	884 (91.7)	1,492 (96.6)
Statin (%)	2,253 (89.8)	842 (87.3)	1,411 (91.3)

Data are presented as number/total number (%) or means ± standard deviations.

ACS = acute coronary syndrome; CAD = coronary artery disease; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; ISR = in-stent restenosis; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST segment elevation myocardial infarction; SA = stable angina; STEMI = ST segment elevation myocardial infarction; UA = unstable angina.

*Body mass index is the weight in kilograms divided by the square of the height in meters.

Table 2. Baseline characteristics of the lesions

Variables	Overall (n=2,666)	De novo (n=978)	ISR (n=1,688)
Number of disease extent (%)			
One-vessel disease	929 (34.8)	342 (35.0)	587 (34.8)
Two-vessel disease	848 (31.8)	331 (33.8)	517 (30.6)
Three-vessel disease	889 (33.3)	305 (31.2)	584 (34.6)
MVD (%)	1,737 (65.2)	636 (65.0)	1,101 (65.2)
Target lesion location (%)			
Left anterior descending artery	1,161 (43.5)	326 (33.3)	835 (49.5)
Left circumflex artery	760 (28.5)	415 (42.4)	345 (20.4)
Right coronary artery	702 (26.3)	230 (23.5)	472 (28.0)
Left main artery	43 (1.6)	7 (0.7)	36 (2.1)
ACC/AHA lesion type B2C (%)	1,202 (45.1)	332 (33.9)	870 (51.5)
Calcification (%)	188 (7.1)	57 (5.8)	131 (7.8)
Bifurcation (%)	574 (21.5)	233 (23.8)	341 (20.2)
Chronic total occlusion (%)	189 (7.1)	61 (6.2)	128 (7.6)
Previous stent type (%)			
Drug-eluting stent 1 st generation			822 (48.7)
Drug-eluting stent 2 nd generation			866 (51.3)
Previous stent diameter (mm)			3.0±0.4
Previous stent length (mm)			27.2±9.3
DCB device (%)			
SeQuent Please	2,534 (95.0)	962 (98.4)	1,572 (93.1)
Pantera Lux	132 (5.0)	16 (1.6)	116 (6.9)
DCB diameter (mm)	2.8±0.4	2.5±0.3	3.0±0.4
DCB length (mm)	22.7±6.4	22.2±5.4	22.9±6.9
DCB total inflation time (min)	49.6±18.8	49.1±17.5	49.9±19.5
DCB maximum pressure (bar)	9.6±3.1	8.6±2.4	10.2±3.3
Dissection after DCB inflation (%)	119 (4.5)	104 (10.6)	15 (0.9)
Bailout stenting (%)	15 (0.6)	12 (1.2)	3 (0.2)
Acute closure (%)	6 (0.2)	1 (0.1)	5 (0.3)
Side branch occlusion (%)	15 (0.6)	5 (0.5)	10 (0.6)
Bleeding all (%)	19 (0.7)	2 (0.2)	17 (1.0)
Procedural success (%)	2,639 (99.0)	957 (97.9)	1,682 (99.6)

Data are presented as number/total number (%) or means ± standard deviations.

ACC/AHA = American College of Cardiology/American Heart Association; DCB = drug-coated balloon; ISR = in-stent restenosis; MVD = multivessel disease.

In 43.5% of the patients, the target lesion was located at the left anterior descending artery (LAD), in 28.5% in the circumflex coronary artery, and 26.3% in the right coronary artery. The SeQuent Please DCB was used in 95% of the patients and Pantera Lux DCB in 5% (Table 2). The mean length of DCBs was 22.7±6.4 mm, with a mean diameter of 2.9±0.5 mm. The mean duration of DCB inflation was 49.6±18.8 seconds. Coronary dissections and bailout stent implantation were observed in 110 (4.5%) and 15 (0.6%) patients, respectively. Procedural success rate was 99.0%. Baseline clinical and procedural characteristics of the study cohort are presented in Tables 1 and 2, respectively.

At 12 months, the primary outcome, TLF, occurred in 179 patients (6.7%); CD was observed in 43 (1.6%), TVMI in 39 (1.5%), and TLR in 137 (5.1%) patients (Table 3, Figure 1). The independent predictors of TLF in the multivariate Cox regression model are summarized in Table 4. A history of hypertension, diabetes mellitus, ACS, previous coronary artery bypass graft (CABG), reduced LVEF, B2C lesion and in-stent restenosis lesion were independent predictors of 12 months TLF in the overall population.

Table 3. Outcomes at 12 months

Variables	Overall (n=2,666)	De novo (n=978)	ISR (n=1,688)
Cardiac death (%)	43 (1.6)	10 (1.0)	33 (2.0)
TVMI (%)	39 (1.5)	2 (0.2)	37 (2.2)
TLR (%)	137 (5.1)	17 (1.7)	120 (7.1)
TLF (%)	179 (6.7)	28 (2.9)	151 (8.9)

Data are presented as number/total number (%).

HR = hazard ratio; IPTW = inverse probability of treatment weighting; ISR = in-stent restenosis; TLF = target lesion failure; TLR = target lesion revascularization; TVMI = target vessel myocardial infarction.

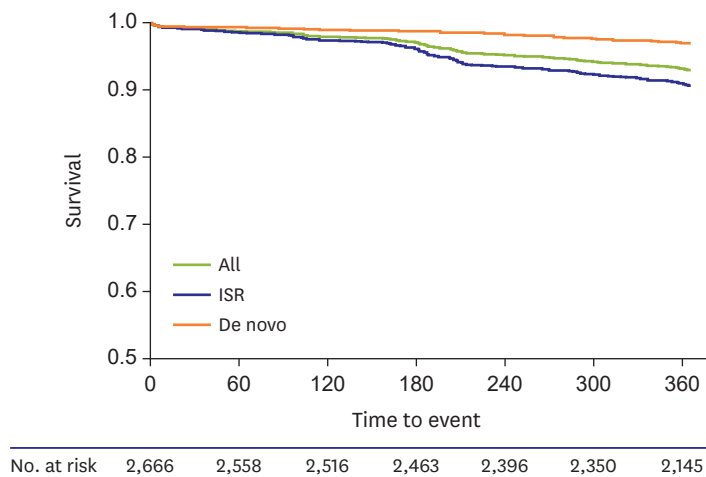


Figure 1. Survival analysis of target lesion failure. ISR = in-stent restenosis.

In-stent restenosis

This study included 1,545 patients with 1,688 ISR lesions. The frequency of cardiovascular risk factors was significantly higher in this group than in patients with de novo lesions except for the frequency of history of current smoking (Table 1). Eight hundred sixty-six (51.3%) of the patients with ISR lesions were treated with a second-generation DES (Table 2). The target lesions in more than half of the patients with ISR lesions were at the LAD. The diameter of the DCB was 3.0±0.4 mm and its length was 22.9±7.2 mm. The incidence of coronary dissection was 0.9% and the rate of bailout stent implantation was 0.2%.

At 12 months, TLF occurred in 151 patients (8.9%); CD was observed in 33 (2.0%), TVMI in 37 (2.2%), and TLR in 160 (7.1%) (Table 3). There were no significant differences of event free survival in patient with ISR lesion according to diabetes mellitus, ACS, multivessel disease (MVD), bifurcation lesion (Figure 2). The history of hypertension, previous CABG, reduced LVEF and B2C lesion were independent predictors of 12 months TLF in patient with ISR lesions (Table 4).

De novo lesions

This study included 964 patients with 978 de novo coronary lesions. Clinical presentation was ACS in 67.4% of these patients. The target lesions were at the left circumflex coronary artery in 42.4% of the patients; 72.4% of the patients had small-vessel disease and 23.8% had bifurcation lesions (Table 2). The mean diameter of DCBs (2.5±0.3 mm) was significantly smaller in the de novo lesion group than in the ISR lesion group, whereas the incidence of coronary dissection (10.6%) and the rate of bailout stent implantation (1.2%) were higher (Table 2).

Table 4. Independent predictors of TLF

Variables	crude HR (95%CI)	crude p value	adjusted HR (95%CI)	adjusted p value
Overall				
Hypertension	2.21 (1.49–3.28)	<0.001	1.81 (1.21–2.7)	0.004
Diabetes mellitus	2.06 (1.48–2.87)	<0.001	1.51 (1.07–2.13)	0.018
Previous CABG	4.1 (2.11–7.96)	<0.001	2.76 (1.39–5.49)	0.004
ACS	0.75 (0.54–1.05)	0.091	0.71 (0.51–0.98)	0.04
LVEF	0.97 (0.96–0.99)	<0.001	0.98 (0.97–0.99)	0.005
eGFR <60 mL/min/1.73m ²	2.19 (1.57–3.06)	<0.001	1.44 (1–2.08)	0.051
B2C lesion	1.41 (1–1.97)	0.047	1.49 (1.06–2.1)	0.023
DCB maximal pressure	1.09 (1.04–1.14)	<0.001	1.05 (1–1.1)	0.054
Lesion: De novo vs ISR	0.31 (0.2–0.47)	<0.001	0.4 (0.26–0.62)	<0.001
ISR				
Hypertension	1.85 (1.21–2.83)	0.005	1.67 (1.09–2.56)	0.019
Diabetes mellitus	1.64 (1.14–2.37)	0.008	1.39 (0.96–2.03)	0.085
Previous CABG	2.99 (1.44–6.21)	0.003	2.55 (1.22–5.36)	0.013
ACS	0.79 (0.55–1.14)	0.206	0.7 (0.49–1.01)	0.058
LVEF	0.98 (0.96–0.99)	0.002	0.98 (0.97–1)	0.016
eGFR <60 mL/min/1.73m ²	1.65 (1.14–2.4)	0.008	1.31 (0.88–1.96)	0.184
B2C lesion	1.59 (1.1–2.3)	0.014	1.57 (1.08–2.28)	0.018
DCB maximal pressure	1.06 (1.01–1.11)	0.025	1.05 (1–1.11)	0.057
De novo				
Current smoking	0.23 (0.05–0.96)	0.043	0.36 (0.08–1.73)	0.204
Hypertension	3.77 (1.31–10.87)	0.014	2.44 (0.73–8.16)	0.147
Diabetes mellitus	3.36 (1.55–7.28)	0.002	2.06 (0.91–4.66)	0.084
Previous CABG	10.2 (2.47–42.08)	0.001	3.65 (0.44–30.52)	0.233
eGFR <60 mL/min/1.73m ²	4.63 (2.19–9.78)	<0.001	2.08 (0.83–5.26)	0.12

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; DCB = drug coated balloon; eGFR = estimated glomerular filtration rate; HR = hazard ratio; ISR = in-stent restenosis; LVEF = left ventricular ejection fraction; TLF = target lesion failure.

At 12 months, TLF occurred in 28 patients (2.9%); CD was observed in 10 (1.0%), TVMI in 2 (0.2%), and TLR in 17 (1.7%) (Table 3). There were no significant differences of event free survival in patient with de novo lesion according to diabetes mellitus, ACS, MVD, bifurcation lesion (Figure 2). There was no independent predictor of 12 months TLF in de novo group (Table 4).

DISCUSSION

In this large-scale multicenter Korean registry study, DCB treatment was applied to all comers with ISR or de novo coronary arterial stenotic lesions. The aim of the study was to evaluate the efficacy and safety of DCB treatment in Korean patients in real-world practice. To the best of our knowledge, this is the largest registry study to demonstrate the safety and efficacy of DCB treatment in this population, especially in patients with de novo lesions. The major findings of this study are as follows: a) DCB treatment in a real-world setting with 2,509 patients was safe and resulted in a low rate of TLF in patients with ISR or de novo lesions; b) a history of hypertension, diabetes, ACS, previous PCI, CABG, reduced LVEF, B2C lesion and ISR lesion were independent predictors of 12 months TLF in the overall study population.

DES are the most widely used devices in treatment of patients with coronary stenosis worldwide owing to their evidence-based safety and efficacy.¹⁾ Despite improvements in the ISR rates, significant limitations remain related to the persisting metallic stent.²⁻⁴⁾ Drug-eluting bioresorbable vascular scaffolds (BVS) have been designed to overcome very late risks of DES.¹⁷⁾ However, the first-generation BVS had a large strut to compensate for the insufficient radial strength of polymer materials, resulting in higher scaffold thrombosis

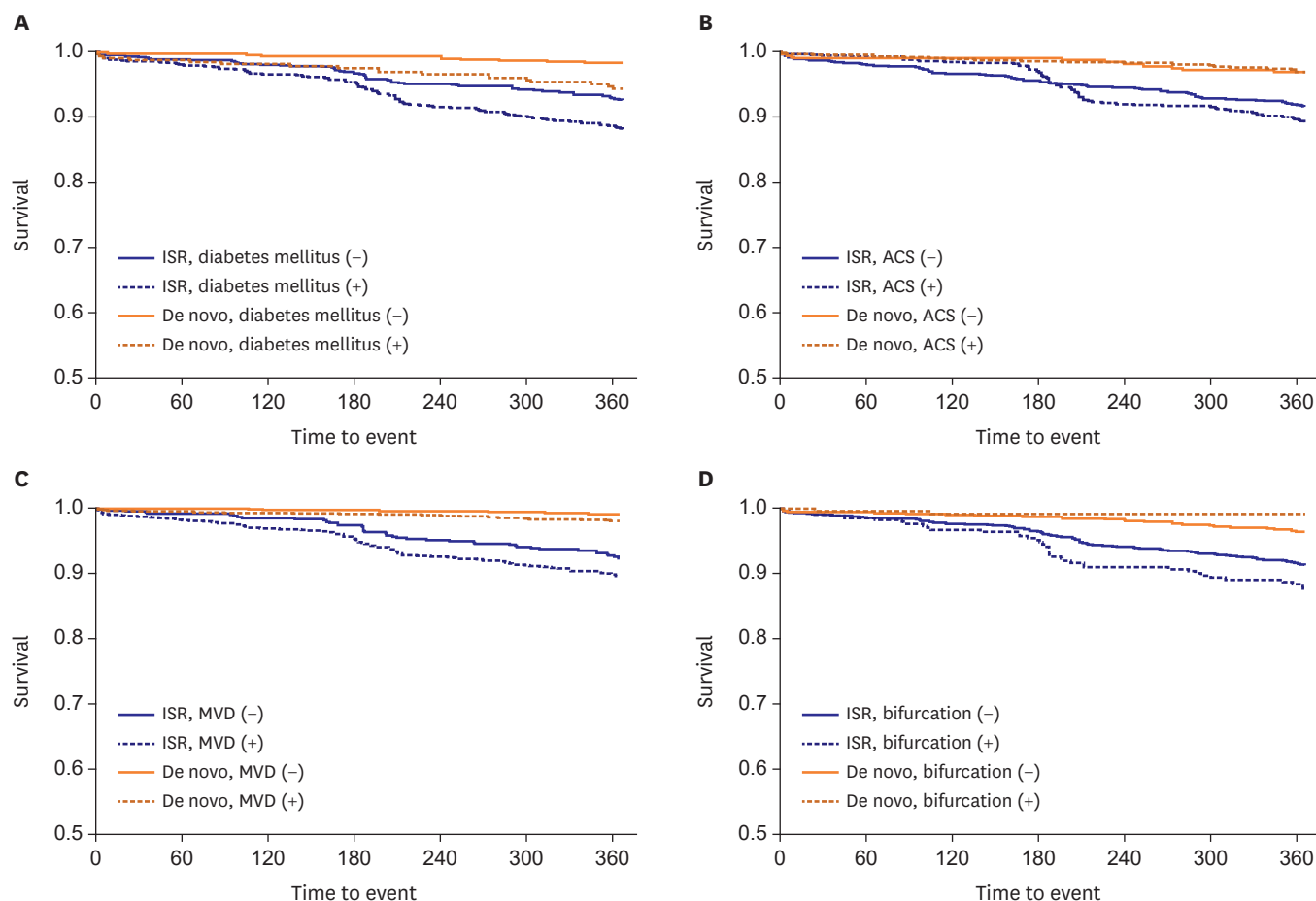


Figure 2. Survival analysis of target lesion failure according to various subgroups. Event free survival according to (A) diabetes mellitus, (B) ACS, (C) MVD, and (D) bifurcation lesion. ACS = acute coronary syndrome; ISR = in-stent restenosis; MVD = multivessel disease.

rates than conventional DES, and was therefore expelled from the market.¹⁸⁾ DCB are another novel concept for overcoming the limitations of DES, especially restenosis of metallic stents.⁴⁾

A large-scale registry study which included more than 2000 patients at 75 sites in 8 countries revealed the safety and efficacy of DCB treatment in real-world practice.¹⁰⁾ The study reported that the rate of major adverse cardiac events (MACEs) was 11.6% in patients with DES ISR and 2.6% in patients with de novo lesions at a 9-month follow-up. The rate of coronary dissection after DCB treatment was 3% in patients with ISR lesions and 8.5% in patients with de novo lesions. Bailout-stent implantation was needed in only 4% of all patients. Jeger et al.¹²⁾ compared the safety and efficacy of DCB with those of DES in patients with small native coronary artery disease. In this randomized trial, 382 patients were assigned to DCB and 376 to DES, and DCB was non-inferior to DES regarding MACE up to 12 months, with similar event rates in both treatment groups (DCB vs. DES: MACE, 7.5% vs. 7.3%; hazard ratio, 0.97 [95% confidence interval, 0.58–1.64], p=0.918).

Studies on the efficacy and safety of DCB treatment in East Asian populations have been limited by moderate numbers of patients. Chen et al. reported the results of The RESTORE ISR China Randomized Trial.¹⁹⁾ In this head-to-head randomized trial, they examined only

240 Chinese patients treated with Restore DEB and SeQuent Please (120 patients per group) and revealed the acceptable efficacy and safety of both DCBs. Habara et al.²⁰ reported the long-term safety and efficacy of DCB treatment in 468 Japanese patients with 550 ISR lesions. Late follow-up (18 months) angiography was performed for 377 (88%) of the remaining 427 lesions (excluding target lesion revascularization), and late restenosis was found in 2 lesions (2.5%) in the BMS-ISR group and 50 lesions (16.8%) in the DES-ISR group. Lee et al.²¹ investigated the effects of procedural optimization on the clinical outcomes of DCB treatment in patients with coronary artery disease. In this analysis, the effect of procedural optimization, including time delay to inflation defined as the delivery time of DCB from the duration between entering the guide catheter and inflation was elucidated.

The incidence of ischemic events was paradoxically lower in East Asian populations than in patients of European descent despite the high prevalence of gene polymorphisms and high on-treatment platelet reactivity in East Asians.²² Lower levels of the inflammatory marker C-reactive protein in East Asians have been observed,²³ and patients of Asian/Pacific Islander descent had a 70% lower prevalence of venous thromboembolism compared to Europeans.²⁴ Bleeding events occurred more frequently in East Asians than in Europeans treated with clopidogrel.²⁵ This low thrombogenicity could partly explain the low incidence of ischemic events in East Asian patients.

In comparison with a previous study with the Western population, this large Korean registry study revealed a relatively low rate of events. These may be partially due to low thrombogenicity in this East Asian population.

DCB treatment in a real-world setting with 2,509 patients was safe and resulted in a low rate of TLF in patients with ISR or de novo lesions. Almost 1,000 patients with de novo coronary lesions were enrolled in this registry study and the mean diameter of DCB was very small (2.5 ± 0.3 mm), whereas previous studies specifically focused on patients with small de novo coronary lesions and were limited by moderate numbers of patients. The incidence of TLF in patients with de novo coronary lesions was low. This finding from large registry data suggests that DCB treatment in patients with small de novo lesions is effective and safe; this result has been well elucidated by various lines of clinical evidence. Considering the efficacy of the DCB-only treatment in small coronary arteries, the treatment of de novo lesions in large coronary arteries seems to be both safe and efficient and the evidence for this is growing. To overcome significant limitations of DES, DCB studies in patients with large de novo coronary lesions seem to be essential. Emerging areas of interest also include drugs other than paclitaxel, the use of physiologic assessment to guide DCB treatment, and DCB use in primary PCI.

There are several limitations to our study. This analysis was based on retrospective, nonrandomized registry data. A comparison with a control group is not possible with such design. Patients and lesions included in this registry were selected, as indicated by ISR, de novo small vessel lesions, and acceptable results of balloon angioplasty. Therefore, the results of this study cannot be generalized to all patients scheduled for coronary intervention. There was no angiographic core lab and qualitative comparative analysis data were not available. Therefore, some important lesion characteristics, for example pre and post reference vessel diameter, lesion length, lumen diameter, and acute gain could not be analyzed, and the frequency and impact of geographic miss cannot be reported. The impact of procedural factors on the occurrence of TLF was not elucidated in this study. The number of TLF

events in the de novo group is small, so the predictive power was weak and no independent predictor was found in this group.

In conclusion, this large multicenter DCB registry study revealed the favorable clinical outcome of DCB treatment in real-world practice in patient with ISR lesion as well as small de novo coronary lesion. Further prospective studies are warranted to confirm the current analyses and define the role and safety of DCB treatment in large de novo coronary artery lesions.

REFERENCES

- Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol* 2015;65:2496-507.
[PUBMED](#) | [CROSSREF](#)
- Gada H, Kirtane AJ, Newman W, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv* 2013;6:1263-6.
[PUBMED](#) | [CROSSREF](#)
- Yamaji K, Räber L, Zanchin T, et al. Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE trial. *Eur Heart J* 2016;37:3386-95.
[PUBMED](#) | [CROSSREF](#)
- Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006;355:2113-24.
[PUBMED](#) | [CROSSREF](#)
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention* 2015;10:1024-94.
[PUBMED](#) | [CROSSREF](#)
- Buccheri D, Piraino D, Andolina G, Cortese B. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. *J Thorac Dis* 2016;8:E1150-62.
[PUBMED](#) | [CROSSREF](#)
- Alfonso F, Scheller B. State of the art: balloon catheter technologies - drug-coated balloon. *EuroIntervention* 2017;13:680-95.
[PUBMED](#) | [CROSSREF](#)
- Kleber FX, Rittger H, Bonaventura K, et al. Drug-coated balloons for treatment of coronary artery disease: updated recommendations from a consensus group. *Clin Res Cardiol* 2013;102:785-97.
[PUBMED](#) | [CROSSREF](#)
- Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87-165.
[PUBMED](#) | [CROSSREF](#)
- Wöhrle J, Zadura M, Möbius-Winkler S, et al. SeQuentPlease World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. *J Am Coll Cardiol* 2012;60:1733-8.
[PUBMED](#) | [CROSSREF](#)
- Yerasi C, Case BC, Forrestal BJ, et al. Drug-coated balloon for de novo coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;75:1061-73.
[PUBMED](#) | [CROSSREF](#)
- Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet* 2018;392:849-56.
[PUBMED](#) | [CROSSREF](#)
- Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing a paclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels: the BELLO (Balloon Elution and Late Loss Optimization) study. *J Am Coll Cardiol* 2012;60:2473-80.
[PUBMED](#) | [CROSSREF](#)
- Cortese B, Di Palma G, Guimaraes MG, et al. Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *JACC Cardiovasc Interv* 2020;13:2840-9.
[PUBMED](#) | [CROSSREF](#)

15. Jeger RV, Eccleshall S, Wan Ahmad WA, et al. Drug-coated balloons for coronary artery disease: third report of the International DCB Consensus Group. *JACC Cardiovasc Interv* 2020;13:1391-402.
[PUBMED](#) | [CROSSREF](#)
16. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237-69.
[PUBMED](#) | [CROSSREF](#)
17. Onuma Y, Serruys PW, Perkins LE, et al. Intracoronary optical coherence tomography and histology at 1 month and 2, 3, and 4 years after implantation of everolimus-eluting bioresorbable vascular scaffolds in a porcine coronary artery model: an attempt to decipher the human optical coherence tomography images in the ABSORB trial. *Circulation* 2010;122:2288-300.
[PUBMED](#) | [CROSSREF](#)
18. Wykrzykowska JJ, Kraak RP, Hofma SH, et al. Bioresorbable scaffolds versus metallic stents in routine PCI. *N Engl J Med* 2017;376:2319-28.
[PUBMED](#) | [CROSSREF](#)
19. Chen Y, Gao L, Qin Q, et al. Comparison of 2 different drug-coated balloons in in-stent restenosis: the RESTORE ISR China randomized trial. *JACC Cardiovasc Interv* 2018;11:2368-77.
[PUBMED](#) | [CROSSREF](#)
20. Habara S, Kadota K, Shimada T, et al. Late restenosis after paclitaxel-coated balloon angioplasty occurs in patients with drug-eluting stent restenosis. *J Am Coll Cardiol* 2015;66:14-22.
[PUBMED](#) | [CROSSREF](#)
21. Lee HS, Kang J, Park KW, et al. Procedural optimization of drug-coated balloons in the treatment of coronary artery disease. *Catheter Cardiovasc Interv* 2021;98:E43-52.
[PUBMED](#) | [CROSSREF](#)
22. Park KW, Lee JM, Kang SH, et al. Safety and efficacy of second-generation everolimus-eluting Xience V stents versus zotarolimus-eluting resolute stents in real-world practice: patient-related and stent-related outcomes from the multicenter prospective EXCELLENT and RESOLUTE-Korea registries. *J Am Coll Cardiol* 2013;61:536-44.
[PUBMED](#) | [CROSSREF](#)
23. Kelley-Hedgpeath A, Lloyd-Jones DM, Colvin A, et al. Ethnic differences in C-reactive protein concentrations. *Clin Chem* 2008;54:1027-37.
[PUBMED](#) | [CROSSREF](#)
24. White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res* 2009;123 Suppl 4:S11-7.
[PUBMED](#) | [CROSSREF](#)
25. Mak KH, Bhatt DL, Shao M, et al. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. *Am Heart J* 2009;157:658-65.
[PUBMED](#) | [CROSSREF](#)