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ORIGINAL ARTICLE

Comparison of 12-month angiographic outcomes between repeat drug-eluting stent implantation and drug-coated balloon treatment for restenotic lesion caused by stent fracture

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Abstract
We aimed to compare the angiographic outcomes between repeat drug-eluting stent (DES) implantation and drug-coated balloon (DCB) treatment for restenotic lesion caused by stent fracture (SF). The treatment of restenotic lesion caused by SF after DES implantation has not been well evaluated. From April 2007 to April 2015, 9320 lesions were implanted with a DES during percutaneous coronary intervention in our hospital; of those, 815 lesions (8.7%) showed restenosis on the follow-up angiogram. The study subjects were 47 consecutive patients with 69 restenotic lesions caused by SF and treated by target lesion revascularization (TLR); of those, 27 patients with 45 lesions were treated with repeat DES during TLR (either a cobalt–chromium or platinum–chromium everolimus-eluting stent or zotarolimus-eluting stent; DES group), and 20 patients with 24 lesions were treated with DCB (DCB group) during TLR. The 12-month cumulative incidence of repeat TLR and predictors of repeat TLR was evaluated. Restenosis and re-restenosis were defined as % diameter stenosis > 50% on the follow-up angiogram. SF was defined as complete or partial separation of the stent strut as assessed by plain fluoroscopy. Baseline characteristics were similar between the groups. The 12-month binary re-restenosis rate and cumulative incidence of repeat TLR between the DES group and DCB group were 44.4% and 37.5% ($p = 0.58$) and 43.9% and 31.9% ($p = 0.31$), respectively. On multivariate analysis, a lesion with vessel hinge movement was an independent predictor of repeat TLR ($p = 0.02$, hazard ratio: 6.54, 95% confidence interval 1.30–32.8). The 12-month repeat TLR rate was high in both groups. After treating restenosis lesions caused by SF after DES implantation, mechanical stress leads to further interventional treatment, regardless of the type of device used.

Keywords Percutaneous coronary intervention · Drug-eluting stent · Drug-coated balloon · Stent fracture

Introduction

During percutaneous coronary intervention (PCI), metal stents are implanted in the coronary artery. However, stent fracture (SF) caused by metal fatigue remains a concern because of its association with restenosis, stent thrombosis (ST), and subsequent target lesion revascularization (TLR) [1, 2] even in the late periods [3]. Although pathological findings and their relevance to cardiovascular events of SF have been previously reported [4], data about repeat interventional treatment for restenotic lesions caused by SF after drug-eluting stent (DES) implantation are limited. Therefore, this study aimed to compare the outcomes between repeat newer-generation durable polymer DES implantation and drug-coated balloon (DCB) treatment for restenotic lesions caused by SF after DES implantation.

Methods

Ethical statements

Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki. The institutional ethics committees approved the study protocol.

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Study population, outcomes measurement, and procedural protocols

From April 2007 to April 2015, 9320 lesions were treated with a DES during PCI in our institution and were followed prospectively. Of 9320 lesions, 7549 lesions had a follow-up angiogram (follow-up rate: 81.0%), and 815 lesions were in-stent restenotic (ISR) lesions (binary restenosis rate 8.7%). Follow-up angiography was performed 8–12 months after primary PCI when patients were able to make regular clinical visits. TLR with PCI was performed when there were symptoms or signs of ischemia and the angiographic diameter of stenosis was ≥ 50%. Of 815 ISR lesions, 81 lesions (9.9%) were found to have SF. After excluding ISR lesions without TLR and angiographic follow-up after TLR, but with TLR with plain balloon angioplasty alone, bare-metal stent, and early-generation DES, 69 lesions (47 patients) had TLR for ISR lesion due to SF after DES implantation, and a newer-generation DES (DES group: 27 patients with 45 lesions) or DCB (SeQuent Please balloon catheter, B. Braun, Melsungen, Germany; DCB group: 20 patient with 24 lesions) was used (Fig. 1).

Baseline demographic and outcomes were evaluated retrospectively between the DES and DCB groups. The primary outcome measure was 1-year repeat TLR after repeat DES implantation or DCB treatment. Coronary angiography was performed routinely at 8–12 months after the repeat intervention.

All interventions were performed using standard techniques. Selection of the type of DES and DCB used in the repeat PCI and use of intravascular imaging devices depended on the operator's discretion. After the procedure, all patients were advised to continue aspirin (100 mg daily) for life, and either ticlopidine (200 mg daily) or clopidogrel (75 mg daily) was prescribed for at least 1 year after stent implantation. Aspirin and ticlopidine/clopidogrel treatment was recommended for at least 3 months in the DCB group, unless the patients had contraindications.

Definitions

Newer-generation DES was defined as a cobalt–chromium everolimus-eluting stent (CoCr-EES), platinum–chromium everolimus-eluting stent (PtCr-EES), slow-release zotarolimus-eluting stent (R-ZES), or thinner biocompatible polymer-coated limus-analog eluting stent. SF was detected in the ISR lesion and defined as complete or partial separation of the stent strut, as assessed by plain fluoroscopy. SF grading was defined according to a previous study: minor fracture (single strut), moderate fracture (multiple strut), and severe fracture (complete separation) [5]. Vessel tortuosity and hinge movement were defined according to previous studies [6, 7]. In all cases of ISR lesions, recurrent ISR lesions occurred in the stent margin and were defined as %diameter stenosis > 50% in the follow-up quantitative coronary analysis (QCA). Patterns of ISR lesions and recurrent ISR lesions were classified on the basis of the Mehran classification [8].

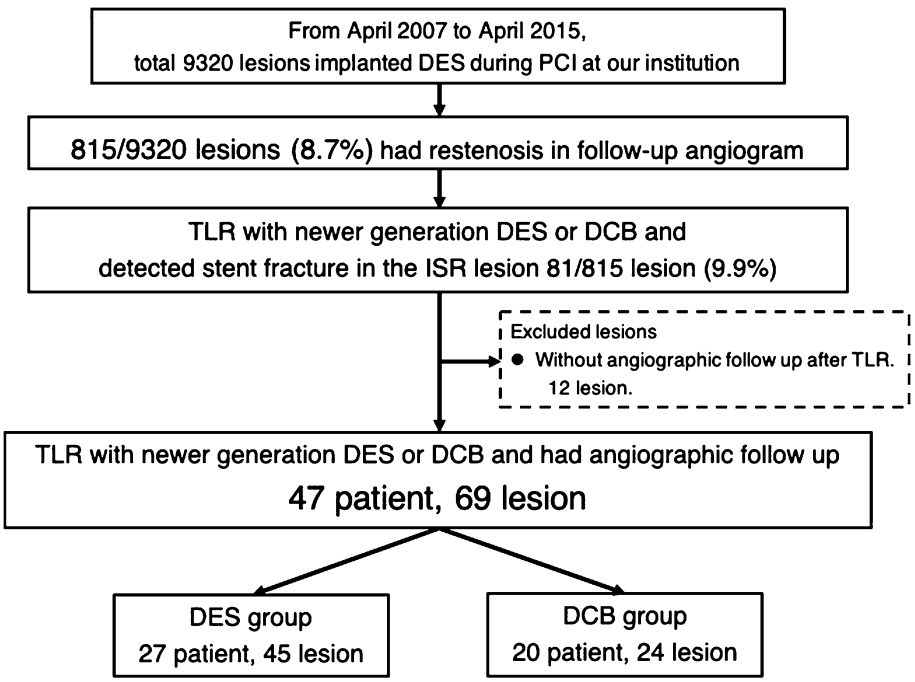

Fig. 1 Study population

QCA

Coronary angiography was performed after intracoronary administration of 0.2 mg of nitroglycerin. The QCA was performed before and after stenting, and during follow-up angiography using a guiding catheter to calibrate the magnification and an automated edge detection algorithm validated by a cardiovascular measurement system (Medis and Heart version 2.0 Cathex, Leiden, The Netherlands). Two or more experienced observers who were blinded to the clinical information performed the QCA independently.

Statistical analysis

Data are presented as a value and percentage, mean, standard deviation, or median (interquartile range). Categorical variables were compared between groups using the v^2 or Fisher's exact test, as appropriate. Continuous variables were compared between groups using Student's paired *t* test or Mann–Whitney' test, according to the normality of data distribution. The primary outcome measure was estimated using Kaplan–Meier's method, and the differences were evaluated with the log-rank test. All statistical analyses were two-tailed, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with the SPSS 11.0 software program (SPSS Inc., Chicago, IL).

A Cox proportional hazard model was used to determine the predictors for repeat TLR. Factors that were indicated by $p < 0.05$ in the univariate analysis were entered into the multivariate regression models. All baseline demographics were entered into the univariate model.

Results

There was no statistically significant difference in the clinical characteristics between the groups (Table 1). Table 2 shows the characteristics of the ISR lesions treated by either a newer-generation DES or DCB and predisposing factors associated with SF. The DCB group included a high number of lesions with vessel hinge movement. Procedural characteristics of repeat PCI for ISR lesions due to SF are shown in Table 3.

The binary recurrent ISR lesion rate and patterns of recurrent ISR lesions are shown in Table 4. The DES group tended to have more total occlusions (40%), whereas the DCB group tended to have more focal re-ISR lesions (67%). Comparisons of the QCA results during the PCI procedure (Table 5) revealed that the postprocedural minimum lumen diameter tended to be small in the DCB group, but there was no significant difference between the two groups.

The primary outcome measure was the cumulative incidence of repeat TLR, and there was no significant difference between the two groups (43.9% versus 31.9%, $p = 0.31$) (Fig. 2). Univariate and multivariate predictors of repeat TLR are shown in Table 6. In the multivariate analysis, severe SF (hazard ratio [HR] 3.18, 95% confidence interval [CI] 0.96–10.6, $p = 0.06$) and lesion with vessel hinge movement (HR 6.54, 95% CI 1.30–32.8, $p = 0.02$) were associated with repeat TLR.

Table 1 Baseline patient characteristics

Variable	DES ($n = 27$)	DCB ($n = 20$)	p value
Age, year	70 ± 13	70 ± 9	0.85
Male, *n* (%)	18 (67)	18 (90)	0.05
Hypertension, *n* (%)	23 (85)	18 (90)	0.63
Diabetes mellitus, *n* (%)	14 (52)	12 (60)	0.59
Dyslipidemia, *n* (%)	13 (48)	11 (55)	0.65
Chronic kidney disease, *n* (%)	14 (52)	12 (60)	0.59
Hemodialysis, *n* (%)	6 (22)	1 (5)	0.08
Previous MI, *n* (%)	4 (15)	2 (10)	0.63
Previous CABG, *n* (%)	1 (4)	1 (5)	0.84

MI myocardial infarction, *CABG* coronary artery bypass graft

Discussion

In this study, we mainly found that angiographic outcomes after additional interventional procedure for restenosis caused by SF were poor and did not differ in terms of treatment devices, i.e., DCB or newer-generation DES implantation.

Repeat revascularization of patients with ISR lesions is challenging [9]. Although several treatment options for ISR lesions after DES implantation exist, the preferred treatment option was reported to be repeat DES implantation instead of conventional angioplasty in the first-generation DES era. However, the 3-year efficacy and safety of the paclitaxel DCB were similar to the paclitaxel-eluting stent in a randomized trial [10]. With regard to the outcomes of CoCr-EES for ISR lesions after DES implantation, Alfonso et al. reported that CoCr-EES provides superior 1-year outcome, i.e., a decreased need for TLR compared with paclitaxel DCB [11].

Recently, the largest meta-analysis of patients with coronary ISR lesions treated with either a second-generation DES or DCB, which included ten studies (4 randomized control trials and 6 observational studies) and examined clinical and angiographic outcomes, demonstrated that a second-generation DES is equally effective and safe as a DCB for TLR, myocardial infarction, and prevention of ST [12].

The development of the DES has revolutionized the field of interventional cardiology, reducing the occurrence of severe

Table 2 Characteristics of ISR lesion

Variable	DES ($n=45$)	DCB ($n=24$)	p value
Location of target lesion			
RCA, *n* (%)	25 (56)	16 (67)	0.37
LAD, *n* (%)	13 (29)	3 (13)	0.10
LCx, *n* (%)	7 (16)	5 (21)	0.60
Restenosis pattern			
Focal, *n* (%)	17 (38)	10 (42)	0.21
Diffuse, *n* (%)	20 (44)	9 (37)	0.32
Total occlusion, *n* (%)	8 (18)	5 (21)	0.18
Grade of SF			
Minor or moderate, *n* (%)	25 (56)	16 (67)	0.36
Severe, *n* (%)	20 (44)	8 (33)	0.36
Lesion complexity			
Calcification, *n* (%)	10 (22)	8 (33)	0.35
Bifurcation, *n* (%)	4 (9)	1 (4)	0.48
RCA ostial, *n* (%)	4 (9)	1 (4)	0.48
Overlap stented lesion, *n* (%) (≥2 stent per lesion)	33 (73)	18 (75)	0.88
Tortuosity, *n* (%)	4 (9)	5 (21)	0.22
Hinge movement, *n* (%)	29 (64)	21 (87)	0.02
DES type			
Sirolimus-eluting stent, *n* (%)	19 (42)	9 (38)	0.72
Pacritaxel-eluting stent, *n* (%)	10 (22)	6 (25)	0.80
Zotarolimus-eluting stent, *n* (%)	5 (11)	1 (4)	0.28
Biorimus A9 eluting stent, *n* (%)	2 (4)	4 (17)	0.15
CoCr-EES, *n* (%)	4 (9)	2 (8)	0.94
R-ZES, *n* (%)	0 (0)	1 (4)	0.33
PtCr-EES, *n* (%)	5 (11)	1 (4)	0.28
Mean stent diameter (mm)	2.86 ± 0.36	2.92 ± 0.41	0.33
Mean total stent length (mm)	24.9 ± 11.5	25.6 ± 14.4	0.73
No. of stents per lesion (*n*)	1.1 ± 0.4	1.2 ± 0.5	0.16

RCA right coronary artery, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery

Table 3 Procedure characteristics at TLR

Variable	DES ($n=45$)	DCB ($n=24$)	p value
DES type			
CoCr-EES, *n* (%)	37 (82)	–	–
R-ZES, *n* (%)	6 (13)	–	–
PtCr-EES, *n* (%)	2 (4)	–	–
Mean stent diameter (mm)	2.86 ± 0.38	–	–
Mean total stent length (mm)	21.2 ± 10.0	–	–
No. of stents per lesion (n)	1.1 ± 0.3	–	–
DCB			
Mean diameter (mm)	–	2.81 ± 0.46	–
Mean total length (mm)	–	22.1 ± 6.8	–
No. per lesion (n)	–	1.0 ± 0.1	–

Table 4 Binary re-ISR rate and patterns of re-ISR

Variable	DES ($n=45$)	DCB ($n=24$)	p value
Binary re-ISR rate, *n* (%)	20 (44)	9 (38)	0.58
Focal, *n* (%)	7 (35)	6 (67)	0.12
Diffuse, *n* (%)	5 (25)	1 (11)	0.41
Total occlusion, *n* (%)	8 (40)	2 (22)	0.37

Table 5 QCA analysis

Variable	DES ($n=45$)	DCB ($n=24$)	p value
Pre-procedure analysis			
MLD (mm)	0.72 ± 0.51	0.73 ± 0.44	0.93
Average RD (mm)	2.53 ± 0.64	2.58 ± 0.57	0.75
%DS (%)	73.9 ± 17.9	72.7 ± 14.8	0.77
Lesion length (mm)	16.2 ± 7.9	15.4 ± 8.0	0.70
Post-procedure analysis			
MLD (mm)	2.44 ± 0.55	2.20 ± 0.48	0.07
Acute gain (mm)	1.76 ± 0.57	1.56 ± 0.69	0.21
%DS (%)	10.8 ± 10.6	15.8 ± 12.6	0.09
Follow-up			
MLD (mm)	1.47 ± 0.98	1.69 ± 0.81	0.42
%DS (%)	49.9 ± 32.4	41.4 ± 28.2	0.36
Late loss (%)	0.98 ± 0.89	0.51 ± 0.99	0.08

MLD minimum lumen diameter, *RD*, reference diameter, *%DS* % diameter stenosis

neointimal proliferation, which is the main cause of restenosis after stent implantation [13]. SF and mechanical issues may be more prevalent in the current DES era. Based on bench test results, Ormiston et al. reported that a stent with cobalt alloys does not fracture easily compared with a stent with thick struts constructed from stainless steel [14]. Additionally, in an autopsy study, Otsuka et al. reported that CoCr-EES had the least incidence of SF compared with an early-generation durable polymer stainless steel DES [4]. Metal alloys or a stent platform resistant to fracture may be suitable for restenotic lesions due to SF. However, further investigation on newer-generation DESs and DCBs in the setting of restenotic lesions caused by SF is needed. An optical coherence tomography study revealed that the absence of a stent strut was the common morphological feature of SF, and its length was correlated with the neointimal area, suggesting that the loss of a stent strut is one of the important contributors to excessive neointimal growth [15]. Additionally, restenosis associated with DES fractures may reflect local trauma sustained by the vessel at

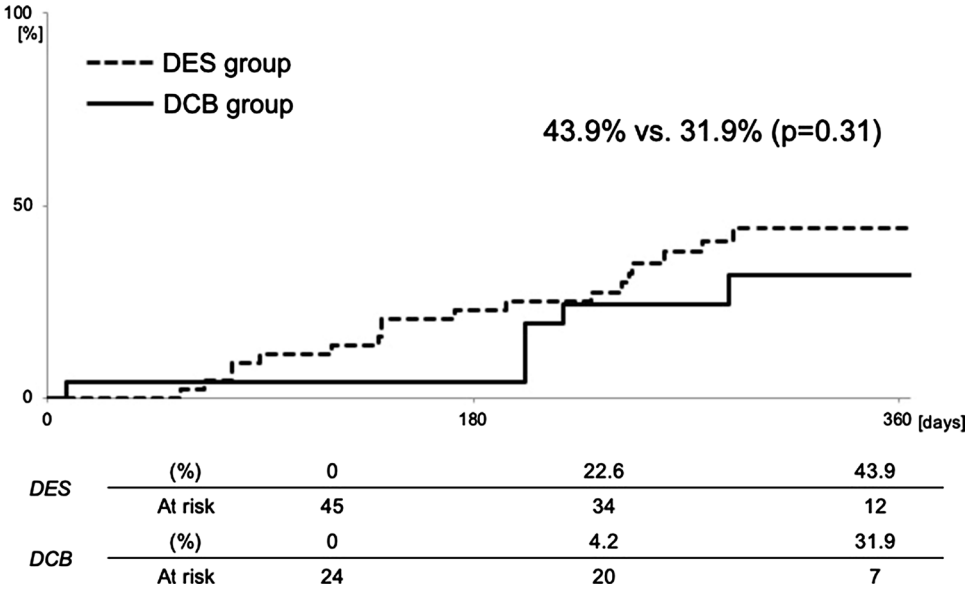

Fig. 2 Cumulative incidence of repeat TLR

Table 6 Predictors of 12 months re-TLR

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Right coronary artery	2.72	1.08–6.88	0.04	0.59	0.17–2.09	0.41
Hinge movement	5.38	1.26–22.9	0.02	6.54	1.30–32.8	0.02
Severe SF	2.56	1.14–5.78	0.02	3.18	0.96–10.6	0.06
Sirolimus-eluting stent ISR	0.27	0.09–0.79	0.02	0.45	0.13–1.60	0.22
Newer generation DES ISR	4.45	1.94–10.2	< 0.01	1.54	0.55–4.33	0.42
Hemodialysis	3.35	1.33–8.45	0.01	2.45	0.81–7.39	0.11

the fracture site. To suppress neointimal growth in such a lesion, a DES and additional stent strut to cover the restenotic lesion to increase the lumen diameter was expected to be the ideal treatment. On the basis of the present study's results, the selection of treatment devices did not lead to the outcomes of such lesions. Lesions with severe SF, which was affected by anatomical specificity such as vessel hinge movement, were predicted to be suitable for further interventional treatment. Regarding the result of recurrent ISR lesion patterns, the DES group tended to have more totally occluded recurrent ISR lesions. The stent-in-stent strategy for a restenotic lesion due to stent fracture might be associated with a high risk for stent thrombosis. However, among the entire study population, there was only one case of stent thrombosis in the DES group. Other totally occluded lesions were silently occluded. There was no case of stent thrombosis in the DCB group. The reason for total occlusion in the DES group might have been the luminal decrease because of the additional metal layer. The totally occluded lesion would become technically complicated and might have needed to be avoided. Considering the current state of interventional cardiology devices for ISR lesions caused by SF from the viewpoint of not adding another metal layer to the coronary artery, DCB treatment might be considered.

Study limitations

First, this study was not a randomized study, and this might have affected the results. The use of a DES or DCB was at the operator's discretion. Second, there was no significant difference in the incidence of 12-month repeat TLR between the two groups. However, the sample size of the present study was small, and the result might be different in a larger population. Lastly, the DCB group included a high number of lesions with vessel hinge movement; however, the angiographic outcomes were similar between the DES group and DCB group, which may indicate that the DCB group showed similar angiographic outcomes in patients with a complicated lesion background.

Conclusions

The 12-month repeat TLR rate was high in both groups. After treating ISR lesions caused by SF after DES, mechanical stress leads to further interventional treatment regardless of the type of treatment devices used during TLR. Further

investigation and newer devices are expected to improve angiographic outcomes to overcome ISR lesions due to SF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no financial relationships or other conflicts of interest relevant to the contents of this paper.

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