

# Comparison of drug-eluting balloon with repeat drug-eluting stent for recurrent drug-eluting stent in-stent restenosis

Guozhong Wang, Quanming Zhao, Qing Chen, Xiaoxia Zhang, Lei Tian and Xiaojiang Zhang

**Objective** Approximately, 10–20% of patients with drug eluting stent (DES) in-stent restenosis (ISR) will develop recurrent ISR; yet, the optimal management of recurrent DES-ISR is unknown. We sought to compare the outcomes of recurrent DES-ISR treated with drug eluting balloons (DEB) to those with repeated implantation of new-generation DES.

**Methods** A total of 172 patients with recurrent DES-ISR were enrolled and stratified into two cohorts: the repeated DES implantation (Re-DES) group and the DEB group. The primary endpoint was the 1-year incidence of major adverse cardiovascular events (MACE).

**Results** Ninety-three patients treated with DEB and 79 patients with Re-DES implantation were analyzed. Both groups had comparable baseline characteristics. Lesser residual stenosis was achieved in the Re-DES group ( $11.3 \pm 3.2\%$  vs.  $22.4 \pm 4.3\%$ ;  $P = 0.00$ ) than in the DEB group. However, the incidence of MACE and target lesion revascularization (TLR) were less in the DEB group ( $17.2\%$  vs.  $32.9\%$ ;  $P = 0.02$  and  $15.1\%$  vs.  $27.8\%$ ;  $P = 0.04$ , respectively). For the  $\geq 3$  metal-layered DES-ISR subgroup, DEB drastically reduced the incidences of MACE and TLR compared with Re-DES ( $20.0\%$  vs.  $57.9\%$ ;  $P = 0.02$  and

$16.0\%$  vs.  $47.4\%$ ;  $P = 0.04$ , respectively). Survival analysis demonstrated that MACE-free survival was significantly higher in the DEB group compared with the Re-DES group, whether the metal layers were  $\geq 3$  or 2. Multivariate analysis revealed that the risk factors of MACE were diabetes mellitus,  $\geq 3$  metal-layered DES ISR, and repeat DES deployment.

**Conclusions** For recurrent DES-ISR, DEB may improve clinical outcomes compared with Re-DES implantation, especially for  $\geq 3$  metal-layered DES-ISR. *Coron Artery Dis* 30: 473–480 Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.

Coronary Artery Disease 2019, 30:473–480

**Keywords:** drug eluting stent, drug eluting balloon, percutaneous coronary intervention, restenosis

Cardiology Department, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, ROC

Correspondence to Guozhong Wang, MD, Cardiology Department, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung, and Blood Vessel Diseases, 2 Anzhen Road, Chaoyang District, Beijing 100029, ROC  
Tel: +86 10 64456747; fax: +86 10 64456313; e-mail: wgz1974@hotmail.com

Received 26 December 2018 Accepted 20 July 2019

## Introduction

The use of drug eluting stents (DES) remains state-of-the-art for percutaneous coronary intervention (PCI), because it drastically reduces the rate of in-stent restenosis (ISR) compared with bare metal stents (BMS) [1,2]. However, DES-ISR still develops in 5–10% of patients after DES deployment [3,4], and DES-ISR has become a common clinical challenge even with the widespread application of new-generation DES [5,6]. Moreover, in comparison with BMS ISR, DES-ISR treatment is associated with worse long-term outcomes; current data suggest that 10–20% of these patients will go on to develop recurrent ISR after repeated stenting [7,8].

Recurrent DES-ISR poses a significant clinical challenge for interventional cardiologists. There are many different therapeutic modalities [such as new DES

repeated implantation, drug eluting balloon (DEB) dilation, excimer laser angioplasty, and brachytherapy] that have been used in patients presenting with recurrent DES-ISR [5,9]; however, the optimal management of these patients remains undefined. Repeated additional DES implantation for recurrent DES-ISR is performed as a default option by many operators, but it is worrisome that multiple metal layers can themselves result in luminal narrowing and stent thrombosis [10]. A new strategy for BMS-ISR and DES-ISR treatment is DEB angioplasty; research has demonstrated that the DEB is associated with more favorable outcomes compared with other conventional treatment modalities [8,9]. DEB is an attractive strategy for recurrent DES-ISR because it can avoid additional metal layers and long duration dual anti-platelet therapy (DAPT). However, there are few studies on recurrent DES-ISR treated with DEB, and the results are controversial [10–12]. The aim of this study was to investigate the clinical outcomes of recurrent DES-ISR treatment with DEB compared with repeated new-generation DES implantation.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

## Methods

### Study population

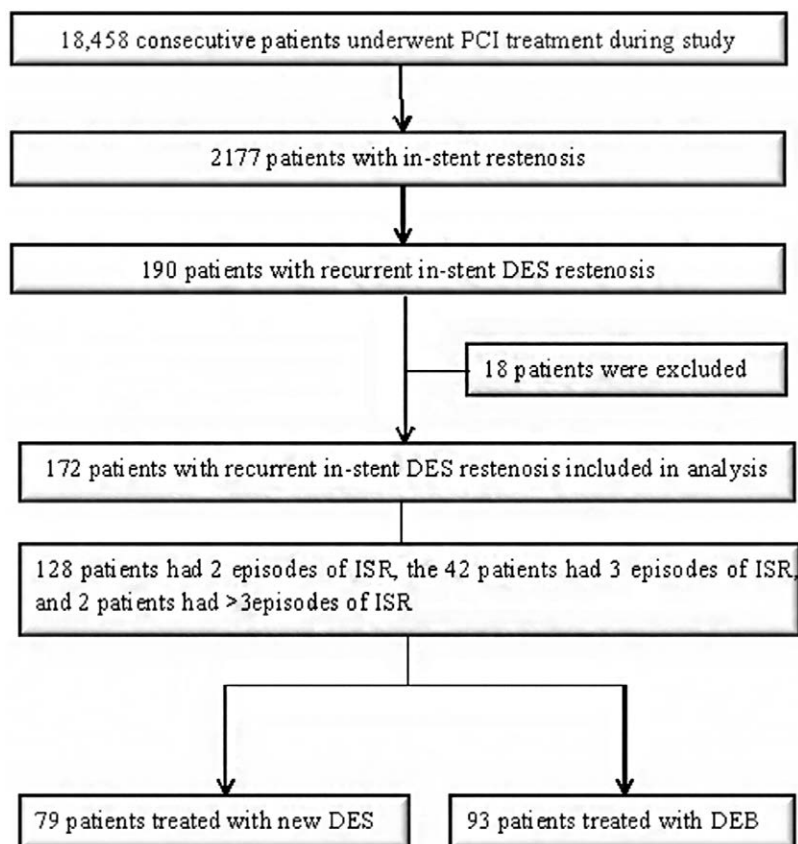
Following institutional review board approval, patients with angina symptoms or ischemia on noninvasive tests undergoing a PCI procedure for recurrent ISR between January 2014 and March 2016 at Beijing Anzhen hospital, Capital Medicine University (Beijing, ROC) were chronologically searched in our hospital database. The baseline clinical characteristics, details of prior PCI, laboratory results, procedural information, and in-hospital clinical events were reviewed comprehensively. Only those patients whose treatment strategy for prior ISR was DES deployment were included in this retrospective study; however, the index stents could be BMS or DES. Patients with any of the following were excluded from the analysis: (1) primary PCI during acute stent thrombosis (ST)-elevation myocardial infarction; (2) severe left ventricular dysfunction (ejection fraction <30%); (3) discontinuation of the DAPT regimen during the first 12 months after DES implantation; (4) treatment with both DEB and DES; (5) unavailable information about prior PCI procedures. The patients with recurrent DES-ISR

were stratified into two main cohorts: those treated with repeated new-generation DES deployment and those with DEB angioplasty. The patient flow is illustrated in Fig. 1. All patients provided written informed consent for data collection and analysis.

### Procedures

All PCIs were performed by certified interventional cardiologists in accordance with the standard procedures in our catheterization laboratory. All of the patients received a loading dose of aspirin and a thienopyridine agent before their arrival in the catheterization room. The PCI was performed via femoral or radial access, using unfractionated heparin or bivalirudin anticoagulation, as per the operator's preference. Adequate lesion preparation was achieved by predilation using either a noncompliant balloon, scoring balloon/cutting balloon, or both. Repeated DES deployment or DEB dilation also was left to the operator's discretion. In the repeated DES implantation (Re-DES) group, new-generation DES was deployed repeatedly after lesion predilation,

Fig. 1



Study flow chart. Between January 2014 and March 2016, a total of 172 consecutive patients with recurrent DES-ISR were assessed in our analysis. In the entire cohort, 128 patients had two episodes of ISR, 42 patients had three episodes of ISR, and two patients had >3 episodes ISR. Among these 172 patients, 79 patients were treated with repeated DES implantation, whereas the remaining 93 patients were treated with DEB. DEB, drug eluting balloon; DES, drug eluting stent; ISR, in-stent restenosis.

and postdilation at high pressures using noncompliant balloon was done routinely. Second-generation DES in this study included everolimus-eluting stents (Xience Prime, Abbott Vascular, Santa Clara, California, USA; PROMUS Element, Boston Scientific Corp., Natick, Massachusetts, USA) and a zotarolimus-eluting stent (Endeavor Resolute, Medtronic Vascular, Santa Clara, California, USA). For the DEB group, after lesion preparation, the DEB was inflated at a nominal pressure for a minimum of 30–60 s to assist drug delivery to the vessel wall. The DEB group used only PEB Sequent Please (B. Braun, Melsulgen, DE) in this study. Every angiography was reviewed and quantitative coronary angiographic (QCA) analysis (Cardiovascular Angiography Analysis System, version 2.0, Pie Medical Imaging, the Netherlands) was performed by an experienced cardiologist, who was blinded to the clinical outcome. The reference vessel diameter, the baseline minimum lumen diameter (MLD), lesion length, and percentage diameter stenosis (DS) were measured, and the postprocedure MLD and residue DS also were measured.

After the procedure, the patients in the Re-DES group received DAPT with aspirin and a thienopyridine agent for at least 1 year, and in the DEB group, DAPT was suggested for at least 1 month. Lifelong low-dose aspirin was recommended for all patients. Follow-up data were gathered during either hospital visits or by phone by professional medical staff at 30 days, 3 months, 6 months, and 1 year after the procedure. No angiographic follow-up was scheduled between 6 and 12 month except for the cases where noninvasive evaluation or clinical presentation suggested the presence of ischemia.

### Outcomes

The primary endpoint was the 1-year incidence of major adverse cardiovascular (CV) events (MACE), which was defined as the composite of death from CV causes, nonfatal myocardium infarction, ischemia-driven target lesion revascularization (TLR), and stent thrombosis. All deaths were considered CV causes unless an unequivocal non-CV cause could be confirmed. We defined myocardium infarction according to the Third Universal Definition of Myocardial Infarction [13], and we defined stent thrombosis according to the definite or probable criteria of the Academic Research Consortium [14]. We defined TLR as needing either percutaneous or surgical revascularization involving the stented segment or within 5 mm of the proximal or distal end of the stent.

### Statistical analysis

The data are presented as the mean  $\pm$  SD for continuous variables and as the percentage or proportions for categorical variables. The clinical characteristics of the two groups were compared with the *t*-test or the Wilcoxon rank-sum score for continuous variables, as appropriate. The  $\chi^2$  test or Fisher exact test was used to analyze

categorical variables. Comparisons of event-free survival (Kaplan–Meier curves) were performed with the log-rank test. Multivariate Cox regression analysis was performed to evaluate the independent predictors of MACE during the follow-up period. All of the *P* values were two-sided, and a *P* value  $<0.05$  was considered statistically significant. The statistical analysis was performed using SPSS version 21.0.0 (IBM Corp., Armonk, New York, USA).

### Results

Within the study period, 18 458 consecutive patients underwent PCI treatment at Beijing Anzhen Hospital, Capital Medicine University (one of the largest tertiary CV disease centers in the ROC), of these patients, 190 were treated for recurrent ISR. As illustrated in Fig. 1, 18 patients were excluded from our analysis: these included three patients due to severe left ventricular dysfunction (ejection fraction  $<30\%$ ); two patients due to premature discontinuation of DAPT after DES implantation; seven patients treated with both DEB and DES; and six patients were excluded because the information about prior PCI procedures was unavailable. In total, 172 patients were included into our study. There was no patient with  $>1$  lesion of recurrent DES-ISR. Another DES deployment was the only strategy for all prior ISR, while the type of stents for the index procedure was unclear in some of included patients. Among the 172 patients, 79 patients were treated with repeat new-generation DES implantation, whereas the remaining 93 patients were treated with DEB. The ISR episodes of the enrolled patients are shown in Fig. 1. Among them, 19 patients in Re-DES group had  $\geq 3$  episodes of ISR, and 25 patients in DEB group had  $\geq 3$  ISR episodes. The frequency was similar in both groups. All procedures were successful with no intrahospital mortality or major complications.

Baseline clinical, lesion, and procedural characteristics of patients with recurrent ISR are summarized in Tables 1

**Table 1** Baseline clinic characteristics of the study population

	Re-DES group (n = 79)	DEB group (n = 93)	<i>P</i> value
Age (year)	66.5 $\pm$ 11.2	67.3 $\pm$ 13.4	0.67
Male sex (n, %)	51 (64.6%)	61 (65.6%)	0.87
Diabetes mellitus (n, %)	26 (32.9%)	31 (33.3%)	1.0
Hypertension (n, %)	49 (62.0%)	56 (60.2%)	0.87
Current smoker (n, %)	25 (31.6%)	32 (34.4%)	0.79
Hypercholesterolemia (n, %)	50 (63.3%)	59 (63.4%)	1.0
Previous MI (n, %)	9 (11.4%)	12 (12.9%)	0.82
Prior coronary bypass surgery (n, %)	3 (3.8%)	4 (4.3%)	1.0
Renal insufficiency (n, %)	10 (12.7%)	12 (12.9%)	1.0
Left ventricular ejection fraction (%)	42.6 $\pm$ 12.3	45.2 $\pm$ 14.6	0.32
Acute coronary syndrome (n, %)	26 (33.1%)	28 (30.1%)	0.62
Peak troponin I (ng/ml)	0.47 $\pm$ 0.32	0.52 $\pm$ 0.46	0.42
hs-CRP (mg/l)	2.9 $\pm$ 1.3	3.3 $\pm$ 1.6	0.08
BNP (pg/ml)	142.5 $\pm$ 24.3	138.6 $\pm$ 33.2	0.37
Thienopyridine agent (n, %)			
Ticagrelor	26 (32.9%)	30 (32.3%)	1.0
Clopidogrel	53 (67.1%)	63 (67.7%)	

BNP, B-type natriuretic peptide; DEB, drug eluting balloon; DES, drug eluting stent; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; PCI, percutaneous coronary intervention.

and 2. In brief, both groups were comparable in most of the baseline clinical features. No significant differences were noted between the two groups in risk factors for coronary heart disease, such as sex, age, smoking, hypertension, or dyslipidemia. Of the total 172 patients, 33.1% had diabetes mellitus, 12.2% had a previous myocardial infarction (MI), and 12.8% had renal insufficiency. It was noteworthy that the proportion of patients who presented with acute coronary syndrome was quite high in both groups (33.1% in the Re-DES group vs. 30.1% in the DEB group;  $P = 0.62$ ).

With respect to lesion characteristics, there was no significant difference with respect to vessel diameter, mini-luminal diameter, lesion length, Mehran's classification of lesion type, and prior stent diameter or length between both groups. It was worth noting that those patients with two episodes of ISR had only two layers of metal at the lesion location, whereas one quarter of patients with multiple recurrences of ISR in our study had  $\geq 3$  metal-layered DES-ISR (24.1% in the Re-DES group vs. 26.9% in the DEB group;  $P = 0.94$ ). In addition, more than half of the last failed stents were second-generation DES, and the frequency was similar in both groups.

For the lesion preparation, the use of noncompliant balloons was similarly common in both groups. However, scoring/cutting balloons was used more frequently in the DEB group (89.2%) than in the DES group (43.0%;  $P = 0.00$ ). Overall, IVUS assessment was performed in just more than half of patients (51%, 89/172); IVUS usage was quite low. Moreover, the QCA measurements demonstrated that the DES group gained better acute

postprocedure results compared with the DEB group (MLD,  $2.67 \pm 0.23$  mm vs.  $2.51 \pm 0.34$ ,  $P = 0.00$ ; DS,  $11.3 \pm 3.2\%$  vs.  $22.4 \pm 4.3\%$ ,  $P = 0.00$ , respectively).

Clinical follow-up was obtained for all patients. The median follow-up period was 460 [interquartile range: 378–650] days. Two patients died at 56 days and 187 days after DES deployment and one patient died at 231 days after DEB angioplasty, with no significant difference between the two groups (2.5% in the Re-DES group vs. 1.1% in the DEB group;  $P = 0.56$ ). Clinical outcomes appeared to be more favorable in the DEB group with regard to both MACE and TLR (Table 3). The cumulative incidence rate of MACE was 17.2% for the DEB group, which was significantly lower than the 32.9% for the DES group ( $P = 0.02$ ). MACE rates were mainly driven by TLR in both groups; the TLR rate was significantly lower in the DEB group (15.1% vs. 27.8%;  $P = 0.04$ ). Moreover, it was noted that both the 1-year MI and ST rates in the DEB group were numerically lower than those in the Re-DES group. The Kaplan–Meier survival analysis (Fig. 2a) revealed that 1-year MACE was significantly lower in patients treated with DEB [ $P = 0.007$ , hazard ratio: 0.43, 95% CI: (0.23–0.79)].

When patients were divided into two groups on the basis of layers of metal at lesions site, 44 patients with  $\geq 3$  metal-layered DES-ISR were associated with much higher incidence of MACEs than the patients with two metal-layered DES-ISR [36.4% (16/44) vs. 20.3% (26/128);  $P = 0.04$ ] (Table 4). Moreover, if those patients with  $\geq 3$  metal-layered DES-ISR were treated with new-DES implantation again, the rates of TLR and MACE were

**Table 2** Procedural characteristics of the study population

		Re-DES group (n = 79)	DEB group (n = 93)	P value
Targeted vessel (n, %)	LM	4 (5.0%)	3 (3.2%)	0.94
	LAD	31 (39.2%)	38 (40.9%)	
	LCX	17 (21.5%)	20 (21.5%)	
	RCA	27 (34.2%)	32 (34.4%)	
Mehran's classification of lesion type [15] (n, %)	Focal	27 (34.2%)	31 (33.3%)	0.99
	Diffuse	22 (27.8%)	26 (27.9%)	
	Proliferative	19 (24.1%)	22 (23.7%)	
	Occlusion	11 (13.9%)	14 (15.1%)	
RVD (mm)		$2.79 \pm 0.53$	$2.65 \pm 0.67$	0.13
Lesion length (mm)		$19.3 \pm 8.5$	$18.7 \pm 7.9$	0.63
MLD before (mm)		$0.57 \pm 0.08$	$0.55 \pm 0.07$	0.08
DS before (%)		$69.7 \pm 7.9$	$71.3 \pm 8.3$	0.20
Prior stent length (mm)		$25.1 \pm 7.3$	$24.9 \pm 6.8$	0.85
Prior stent diameter (mm)		$2.83 \pm 0.32$	$2.76 \pm 0.25$	0.11
Prior type of stent (n, %)	First-generation DES	28 (35.4%)	35 (37.6%)	0.87
	Second-generation DES	51 (64.6%)	58 (62.4%)	
$\geq 3$ metal-layered ISR (n, %)		19 (24.1%)	25 (26.9%)	0.73
Noncompliance balloon usage (%)		79 (100%)	91 (97.8%)	0.94
Scoring/cutting balloon usage (%)		34 (43.0%)	83 (89.2%)	0.00
DES or DEB diameter (mm)		$2.91 \pm 0.43$	$2.83 \pm 0.36$	0.19
DES or DEB length (mm)		$26.3 \pm 5.8$	$24.7 \pm 6.9$	0.11
MLD (mm) after		$2.67 \pm 0.23$	$2.51 \pm 0.34$	0.00
DS(%) after		$11.3 \pm 3.2\%$	$22.4 \pm 4.3\%$	0.00
IVUS usage (n, %)		42 (53.2%)	47 (50.5%)	0.54
Thienopyridine agent (n, %)	Clopidogrel	51 (64.6%)	64 (68.8%)	0.55
	Ticagrelor	28 (35.4%)	29 (31.2%)	

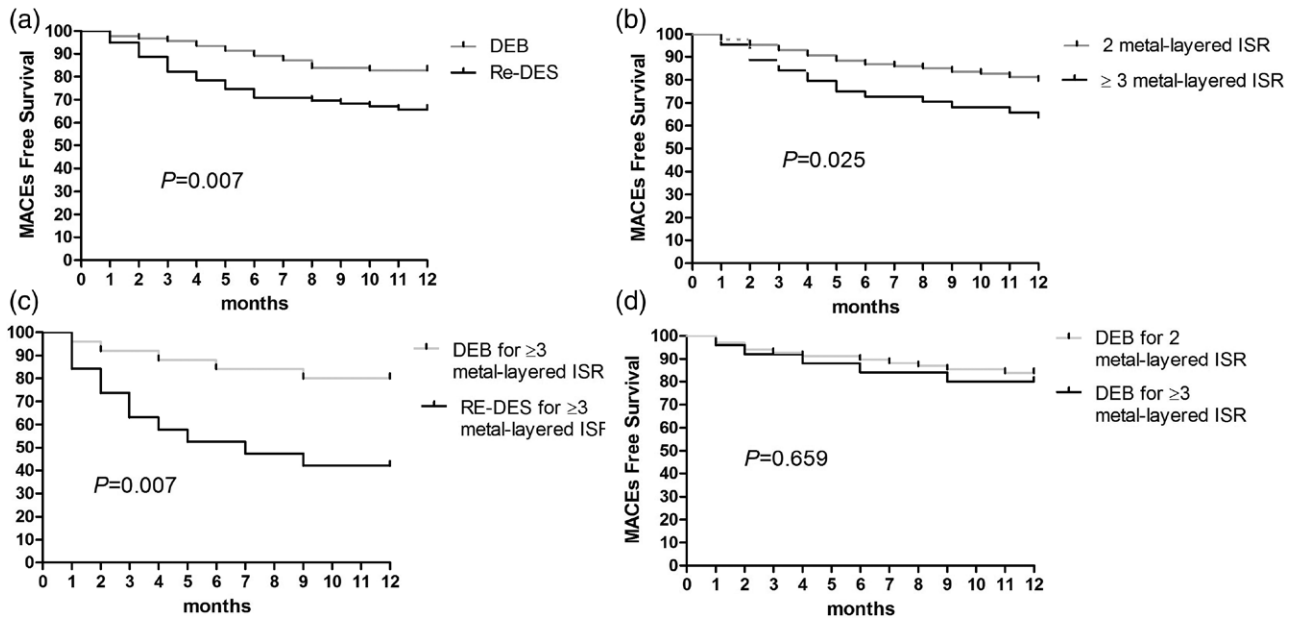
DS, percentage diameter stenosis; DEB, drug eluting balloon; DES, drug-eluting stent; ISR, in-stent restenosis; IVUS, intravascular ultrasound; LAD, left anterior descending; LCX, left circumflex; LM, left main; MLD, minimum luminal diameter; RCA, right coronary artery; RVD, reference vessel diameter.

**Table 3** The 1-year major adverse cardiovascular events of the repeated drug eluting stent group vs. the drug eluting balloon group (n, %)

	Re-DES group (n = 79)	DEB group (n = 93)	Hazard ratio (95% CI)	P value
MACEs	26 (32.9%)	16 (17.2%)	1.13–2.14	0.02
Death	2 (2.5%)	1 (1.1%)	0.64–3.26	0.59
Myocardial infarction	9 (11.4%)	6 (8.7%)	0.85–2.10	0.29
STEMI	2 (2.5%)	1 (1.1%)	0.64–3.31	0.59
NSTEMI	7 (8.9%)	5 (5.4%)	0.78–2.16	0.39
TLR	23 (27.8%)	14 (15.1%)	1.08–2.07	0.04
Definite/probable stent thrombosis	3 (3.8%)	2 (2.2%)	0.64–2.78	0.66

CI, confidence interval; DEB, drug eluting balloon; DES, drug eluting stent; MACE, major adverse cardiovascular events; NSTEMI, non-ST-elevation myocardial infarction; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization.

**Fig. 2**



Kaplan–Meier MACE-free survival curves for the patients with recurrent DES-ISR during 1-year follow-up. (a) Comparison of MACE-free survival for patients with the recurrent DES-ISR between those treated with DEB and those treated with repeated DES implantation (log-rank test,  $P = 0.007$ ). (b) Comparison of MACE-free survival between the patients with  $\geq 3$  metal-layered DES-ISR and patients with two metal-layered DES-ISR (log-rank test,  $P = 0.025$ ). (c) Comparison of MACE-free survival for the patients with  $\geq 3$  metal-layered DES-ISR between treated with DEB and treated with repeated new DES implantation (log-rank test,  $P = 0.007$ ). (d) Comparison of MACE-free survival between the patients with  $\geq 3$  metal-layered DES-ISR and two metal-layered DES-ISR treated with DEB identically (log-rank test,  $P = 0.659$ ). CV, cardiovascular; DEB, drug eluting balloon; DES, drug eluting stent; ISR, in-stent restenosis; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularization.

**Table 4** The 1-year major adverse cardiovascular events of patients with different metal-layered drug eluting stent in-stent restenosis (n, %)

	$\geq 3$ metal-layered ISR (n = 44)	2 metal-layered ISR (n = 128)	Hazard ratio (95% CI)	P value
MACEs	16 (36.4%)	26 (20.3%)	1.06–3.01	0.04
Death	1 (2.5%)	2 (0.8%)	0.14–15.66	1.00
Myocardial Infarction	4 (9.1%)	11 (8.6%)	0.35–3.15	1.00
STEMI	1 (2.3%)	2 (1.6%)	0.13–15.66	1.00
NSTEMI	3 (6.8%)	9 (7.0%)	0.78–2.16	1.00
TLR	13 (29.5%)	24 (18.8%)	0.88–2.82	0.14
Definite/probable stent thrombosis	2 (4.5%)	3 (2.3%)	0.33–11.23	0.60

CI, confidence interval; DEB, drug eluting balloon; DES, drug eluting stent; MACE, major adverse cardiovascular events; NSTEMI, non-ST-elevation myocardial infarction; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization.

as high as 47.4% (9/19) and 57.9% (11/19), which were significantly higher than the remaining patients treated with DEB [47.4% vs. 16.0% (4/25),  $P = 0.04$  and 57.9% vs. 20.0% (5/20),  $P = 0.01$ , respectively] (shown as Table 5). The Kaplan–Meier survival analysis (Fig. 2b, c) revealed similar trends. However, survival analysis demonstrated that if the patients were treated with DEB, there was no significant difference between the patients with  $\geq 3$  metal-layered DES-ISR and the patients with two metal-layered DES-ISR (Fig. 2d).

For the final multivariable analysis, the diabetes mellitus, hyper-cholesterolemia, Mehran's classification of lesion type, episodes of restenosis, the lesion length, MLD (before), DS (before), postprocedure MLD, residue DS, Scoring/Cutting balloon usage, and the Re-DES deployment were included into the final analysis model because these factors were considered to be clinically important or  $P < 0.10$  as univariate analysis. The multivariable analysis revealed that the following were risk factors of MACE: diabetes mellitus [hazard ratio, 2.21; (95% CI, 1.12–4.36);  $P = 0.02$ ],  $\geq 3$  metal-layered DES-ISR [hazard ratio, 3.51; (95% CI, 1.84–6.23);  $P = 0.04$ ], and Re-DES deployment [compared with DEB; hazard ratio, 3.17; (95% CI, 1.75–5.76);  $P = 0.00$ ]. Neither the postprocedure MLD, residue stenosis nor the lesion length was the independent risk factor.

## Discussion

In the present study, it was demonstrated that the rate of MACE in patients with recurrent DES-ISR was quite high after PCI treatments in both groups and was mainly driven by high TLR. Our study also indicated that DEB was associated with more favorable clinical outcomes for recurrent DES-ISR compared with repeated new-generation DES deployment, especially for patients with  $\geq 3$  metal-layered DES-ISR. In addition, this research revealed that with Re-DES deployment,  $\geq 3$  metal-layered DES-ISR and diabetes mellitus were both independent risk factors of MACE, but no other lesion factors or procedure characteristics were predictors of MACE.

For recurrent DES-ISR, the most reasonable treatment option is still uncertain. Theoretically, it is speculated that redeployment of additional stents with multimetallc layers will themselves lead to lumen loss at lesions, especially at small diameter vessels [8,9]. In addition, stent

under-expansion has been reported as a major potential mechanism for DES-ISR [16], while repeat stenting could not correct the existing stent under-expansion with multimetallc layers, but would aggravate this phenomenon and result in worse clinical outcomes. Moreover, too many layers of metal could result in the loss of side branches and damage endothelial function at the stenting segment, which are causes of adverse clinical outcomes [9,10]. Varghese *et al.* [17] reported that in patients with recurrent DES-ISR treated by new-generation DES repeat deployment, the rates of 1-year MACE and TLR were 30.8% and 24.2%, respectively. These were similar to the adverse event rates for the Re-DES group in our study. These results demonstrate that repeat DES stenting is not an optimal option for this challenging subgroup.

Distinct from repeat stenting, DEBs release an antiproliferative drug into the vascular wall, inhibiting intimal hyperplasia and reducing the rate of ISR. This avoids any residual chronic inflammatory response caused by another metal layer and polymers, and thereby decreases the risk of subsequent late thrombosis. Thus, using DEBs as an alternative treatment in this scenario is theoretically advantageous relative to the worse results of recurrent DES-ISR [18]. Kawamoto *et al.* [12] reported that for treating recurrent multilayered-metallic ISR, DEB was not inferior compared with repeat deployment of the new-generation DES, and it was demonstrated that DEBs have a similar effect on recurrent or new-onset DES restenosis [10–12]. In line with those reports, the present study demonstrated that DEB was associated with favorable outcomes compared with repeated new-generation DES deployment, especially because the DEB, compared with Re-DES, drastically reduced the incidences of MACE and TLR for patients with  $\geq 3$  metal-layered DES-ISR. These findings suggest that DEB may be an alternative option for recurrent DES-ISR compared to repeated DES implantation.

Although the DEB was superior to repeating the DES for recurrent DES-ISR in the present study, both modalities provided unsatisfactory clinical outcomes. Therefore, we believe that new exceptional treatment modalities should be sought after to prevent ISR recurrences for these challenging patients. Moreover, the rates of MACE and TLR in both groups were higher than reports from many

**Table 5** The 1-year major adverse cardiovascular events for patients with  $\geq 3$  metal-layered drug eluting stent in-stent restenosis (n, %)

	Re-DES group (n = 19)	DEB group (n = 25)	Hazard ratio (95% CI)	P value
MACEs	11 (57.9%)	5 (20.0%)	1.21–6.93	0.01
Death	1 (5.3%)	0	ND	ND
Myocardial infarction	3 (15.8%)	1 (4.0%)	0.44–35.05	0.30
STEMI	1 (5.3%)	0	ND	ND
NSTEMI	2 (10.5%)	1 (4.0%)	0.25–26.93	0.57
TLR	9 (47.4%)	4 (16.0%)	1.07–8.18	0.04
Definite/probable stent thrombosis	1 (5.3%)	1 (4.0%)	0.09–19.73	1.00

CI, confidence interval; DEB, drug eluting balloon; DES, drug eluting stent; MACE, major adverse cardiovascular events; NSTEMI, non-ST-elevation myocardial infarction; ND, no data; ST, stent thrombosis; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization.

other studies [10–12]. This suggests that the patients in the current study had additional high-risk factors that resulted in adverse effects on the prognosis. First, almost one quarter of the patients in our study had  $\geq 3$  metal-layered restenosis at the same lesions. This would have a negative effect on the treatment of those patients, as our study revealed that the incidences of TLR and MACE in patients with  $\geq 3$  metal-layered DES-ISR were higher than the patients with two metal-layered DES-ISR; this was especially true for patients in the Re-DES group. Furthermore, the patients in our study had many high-risk factors, such as almost one-third of patients presented with ACS and another one-third with diabetes mellitus; these clinical features might affect the prognosis of the patients. In addition, although intravascular ultrasound imaging (IVUS) or optical coherence tomography (OCT) has been considered as a useful adjunctive tool to improve the outcomes of DES-ISR [19,20], the IVUS measurement was only performed in just over half of patients in both groups (53.2% in the Re-DES group vs. 50.5% in the DEB group;  $P = 0.86$ ). Maybe better outcomes could be expected with greater use of intravascular imaging.

The strategy of repeat new DES deployment for recurrent DES-ISR raises a major concern that is the increasing risk of ST [21]. In theory, too many layers of stent strut and polymer may present substrates for stent thrombosis. Moreover, the high dose of antiproliferation drug can inhibit proper endothelial healing, which has been demonstrated to be an independent risk factor for late stent thrombosis [22]. In the present study, there were three ST events in the Re-DES group that occurred at 65 days, 132 days, and 204 days after the index procedure, respectively, and the DAPT was continued at those times. The two ST events in the DEB group were found at 3 days and 213 days after the procedure. The first was considered a residual dissection following the balloon dilation, and the second patient just accepted aspirin when the ST occurred. Although the ST rates in the Re-DES group was nominally higher than the DEB group during the 1-year follow-up [3/79 (3.8%) vs. 2/93 (2.2%);  $P = 0.66$ ], due to the small sample size and short follow-up time in this analysis, a larger RCT study would be required to clarify whether the strategy of Re-DES for recurrent DES-ISR increases the rate of stent thrombosis.

From multivariate analysis, diabetes mellitus, restenosis with  $\geq 3$  stent layers, and Re-DES deployment were found as risk factors of MACE rates in the present study. Whether in the BMS or DES era, diabetes is a predictor of adverse events after stent implantation, which has been repeatedly confirmed by various clinical studies [23,24]. Similarly, for recurrent DES-ISR, diabetes mellitus remains an independent risk factor for adverse events in the present analysis. For the patients with  $\geq 3$  metal-layered DES-ISR (multiple recurrences of restenosis),

previous failures in treatment of ISR indicated that the problems that led to failure of the prior stent would be persistent. If repeat DES deployment is used for treatment of those patients, the persistent problems can be difficult to correct, and may be even amplified by subsequent stents. Our findings verified this speculation to some extent in that the patients with  $\geq 3$  metal-layered DES-ISR were associated with worse outcomes compared with patients with two metal-layered DES-ISR, especially when those patients were treated with new DES deployment. However, if the patients with  $\geq 3$  metal-layered DES-ISR were treated with DEB, then the clinical outcomes were not only better than those with Re-DES implantation, but also were comparable to those of the patients with two metal-layered DES-ISR. These findings suggest that the DEB would be a superior option for a challenging setting such as patients with  $\geq 3$  metal-layered DES-ISR.

This study has some limitations. First, the major limitation of this analysis is its retrospective nature; the decisions on the choice of treatment were not random but based on the operator's preference. Although we did not find significant difference in the lesion or clinical characteristics between groups, the presence of unrecognized confounders is possible. Second, the devices (DES or DEB) used in our study do not cover all previous emerging products, which affects the results of these patients. Finally, this is a small cohort of patients from a single center. Another larger prospective, randomized trial needs to be undertaken to assess both treatment modalities for recurrent DES-ISR.

In conclusion, for recurrent DES-ISR, DEB seems to be associated with more favorable clinical outcomes compared with repeat new-generation DES implantation, especially for patients with  $\geq 3$  metal-layered DES-ISR. We found that diabetes mellitus,  $\geq 3$  metal-layered DES-ISR, and Re-DES deployment were the risk factors of MACE for recurrent DES-ISR. However, the clinical outcomes in both groups were not quite satisfactory; this suggests that more optimal therapeutic modalities for recurrent DES-ISR should be investigated in the future.

### Acknowledgements

The authors acknowledge the expertise of all operators in performing the cardiac catheterization in Beijing Anzhen Hospital, Capital Medical University.

This study was supported by the National Nature Science Foundation of China (NSFC20157843). The funding organization had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

### Conflicts of interest

There are no conflicts of interest.

## References

- 1 Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, *et al.*; SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**:1315–1323.
- 2 Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, *et al.*; TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**:221–231.
- 3 Kedhi E, Joesoef KS, McFadden E, Wassing J, van Mieghem C, Goehart D, Smits PC. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet* 2010; **375**:201–209.
- 4 Harjai KJ, Kondareddy S, Pinkosky B, Harjai N, Orshaw P, Boura J. Everolimus-eluting stents versus sirolimus- or paclitaxel-eluting stents: two-year results from the Guthrie Health off-label stent (GHOST) registry. *J Interv Cardiol* 2013; **26**:153–162.
- 5 Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol* 2014; **63**:2659–2673.
- 6 Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol* 2010; **56**:1897–1907.
- 7 Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García del Blanco B, García-Touchard A, López-Minguéz JR, *et al.*; RIBS IV Study Investigators (under auspices of Interventional Cardiology Working Group of Spanish Society of Cardiology). A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents: the RIBS IV randomized clinical trial. *J Am Coll Cardiol* 2015; **66**:23–33.
- 8 Siontis GC, Stefanini GG, Mavridis D, Siontis KC, Alfonso F, Pérez-Vizcayno MJ, *et al.* Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. *Lancet* 2015; **386**:655–664.
- 9 Alfonso F, Scheller B. Management of recurrent in-stent restenosis: onion skin full metal jacket? *Eurointervention* 2013; **9**:781–785.
- 10 Alfonso F, García J, Pérez-Vizcayno MJ, Hernando L, Hernandez R, Escaned J, *et al.* New stent implantation for recurrences after stenting for in-stent restenosis: implications of a third metal layer in human coronary arteries. *J Am Coll Cardiol* 2009; **54**:1036–1038.
- 11 Kubo S, Kadota K, Otsuru S, Hasegawa D, Shigemoto Y, Habara S, *et al.* Optimal treatment of recurrent restenosis lesions after drug-eluting stent implantation for in-stent restenosis lesions. *Eurointervention* 2013; **9**:788–796.
- 12 Kawamoto H, Rupareliá N, Latib A, Miyazaki T, Sato K, Mangieri A, *et al.* Drug-coated balloons versus second-generation drug-eluting stents for the management of recurrent multilayered in-stent restenosis. *JACC Cardiovasc Interv* 2015; **8**:1586–1594.
- 13 Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, *et al.* Third universal definition of myocardial infarction. *Circulation* 2012; **126**:2020–2035.
- 14 Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the circulatory system medical devices advisory panel of the food and drug administration center for devices and radiologic health, december 7-8, 2006. *Circulation* 2007; **115**:2352–2357.
- 15 Mehran R, Dangas G, Abizaid AS, Mintz GS, Lansky AJ, Satler LF, *et al.* Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 1999; **100**:1872–1878.
- 16 Ferri LA, Jabbour RJ, Giannini F, Benincasa S, Ancona M, Regazzoli D, *et al.* Safety and efficacy of rotational atherectomy for the treatment of undilatable underexpanded stents implanted in calcific lesions. *Catheter Cardiovasc Interv* 2017; **90**:E19–E24.
- 17 Varghese MJ, Bhatheja S, Baber U, Kezbor S, Chincholi A, Chamaria S, *et al.* Intravascular brachytherapy for the management of repeated multilayered drug-eluting coronary stent restenosis. *Circ Cardiovasc Interv* 2018; **11**:e006832.
- 18 Gray WA, Granada JF. Drug-coated balloons for the prevention of vascular restenosis. *Circulation* 2010; **121**:2672–2680.
- 19 Zhang Y, Farooq V, Garcia-Garcia HM, Bourantas CV, Tian N, Dong S, *et al.* Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomised trial and ten observational studies involving 19,619 patients. *Eurointervention* 2012; **8**:855–865.
- 20 Habara M, Terashima M, Nasu K, Kaneda H, Yokota D, Ito T, *et al.* Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study. *Eur Heart J Cardiovasc Imaging* 2013; **14**:276–284.
- 21 Shuchman M. Trading restenosis for thrombosis? New questions about drug-eluting stents. *N Engl J Med* 2006; **355**:1949–1952.
- 22 Finn AV, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, *et al.* Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005; **112**:270–278.
- 23 Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, *et al.* Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol* 1998; **32**:1866–1873.
- 24 Kastrati A, Dibra A, Mehilli J, Mayer S, Pinićek S, Pache J, *et al.* Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation* 2006; **113**:2293–2300.