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Switching types of drug-eluting stents does not prevent repeated in-stent restenosis in patients with coronary drug-eluting stent restenosis

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Objectives **We treated patients experiencing drug-eluting stent (DES) restenosis with plain old balloon angioplasty (POBA), implantation of the same type of DES [homogeneous drug-eluting stent (HOMO-DES)], or implantation of a different type of DES [heterogeneous drug-eluting stent (HETERO-DES)], and compared the efficacy and safety of these procedures for the prevention of repeated in-stent restenosis (ISR).**

Background **In patients with de-novo coronary lesions, DES implantation is associated with a markedly reduced restenosis rate as compared with that associated with a bare metal stent and POBA. However, the optimal management strategy for patients with DES ISR remains unknown.**

Patients and methods **We identified 191 consecutive DES ISR lesions from 183 patients who required clinically driven revascularization and divided them into three groups according to the treatment: 38 lesions were treated with POBA, 38 with HOMO-DES, and 115 with HETERO-DES.**

Results **The incidence of target lesion revascularization (TLR) was 42.1% (16/38), 15.8% (6/38), and 16.5% (19/115) in the POBA, HOMO-DES, and HETERO-DES groups (POBA vs. HOMO, HETERO-DES; $P = 0.002$, respectively). Multivariate analysis indicated that diabetes [odds ratio (OR), 3.4], hemodialysis (OR, 7.74), nonfocal ISR patterns (OR, 3.35), previous myocardial infarction (OR, 3.26), and POBA (OR, 8.84) were independent predictors of TLR.**

Conclusion **A strategy involving repeated DES implantation was superior to POBA for preventing recurrent restenosis. Treatment with a different type or generation of DES does not appear to reduce the incidence of TLR. Moreover, we identified certain useful factors for facilitating appropriate and early triage in the patients with repeated DES ISR.** *Coron Artery Dis* **25:638–644 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: drug-eluting stent, heterogeneous drug-eluting stent, homogeneous drug-eluting stent, in-stent restenosis, switching types (drug coating or generation) of drug-eluting stent

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Introduction

Coronary stenting is more effective for preventing angiographic restenosis than plain old balloon angioplasty (POBA) [1,2]. Although conventional bare metal stents (BMSs) effectively reduce the incidence of acute occlusion following a percutaneous coronary intervention (PCI), the neointimal hyperplasia that develops within 3–6 months of implantation is considered a limitation of this procedure [3,4]. Drug-eluting stents (DESs) were developed to resolve these challenging problems and have clearly yielded good results [5]. However, pivotal, randomized trials comparing DESs with BMSs have shown that DES in-stent restenosis (ISR) still develops in a small number of patients [6–8]. POBA is the first-line treatment option for ISR, which obviates the need for stent-in-stent placement; however, the recurrence rate associated with this technique is often more than 40% [9]. Alternative interventions, including rotational atherectomy, excimer laser angioplasty, directional coronary atherectomy, use of cutting balloons, and brachytherapy, have not yielded any additional benefits [10–14]. Some reports have shown that the use of DESs is superior to brachytherapy for the treatment of ISR occurring within BMSs [15,16]. However, for patients with DES ISR, the optimal management strategy remains unclear. Although there are many possible mechanical-based or lesion-based etiologies for DES restenosis, drug resistance may also play a role [17–20]. Therefore, the deployment of a DES that elutes a different drug could treat DES ISR more effectively than the continued use of the same type of DES. In the present study, we report our experience with three different DES ISR treatment procedures: POBA, the use of the same type of DES, and the use of a different type of DES. In addition, we assessed the efficacy and safety of these three treatments.

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Patients and methods

Study population

Between April 2007 and March 2013, 2784 patients with angina pectoris or evidence of myocardial ischemia (inducible or spontaneous) underwent PCI involving DESs in our institution. Follow-up coronary angiography (CAG) was performed 6 months (range, 160–200 days) after the procedure. All patients continued to take aspirin (100 mg, daily) and ticlopidine (100 mg, twice daily) or clopidogrel [75 mg, daily (the standard dose in Japan)] until the follow-up CAG was performed.

Repeated percutaneous coronary intervention procedure

We identified 191 consecutive restenotic lesions, in 183 patients, which required ischemic-driven revascularization. All patients provided informed consent to participate in this study, which was approved by the Institutional Ethics Committee of our institution and the study was carried out according to the principles of the Declaration of Helsinki. Throughout the study, the physicians used six different types of DESs. The first-generation DESs included sirolimus-eluting stent (SES) (Cypher; Cordis/Johnson & Johnson, Warren, New Jersey, USA) and paclitaxel-eluting stent (PES) (Taxus; Boston Scientific, Natick, Massachusetts, USA). The second-generation DESs included zotarolimus-eluting stent (E-ZES) (Endeavor; Medtronic, Santa Rosa, California, USA), biolimus-eluting stent (Nobori; Terumo, Tokyo, Japan), resolute zotarolimus-eluting stent (R-ZES) (Resolute Integrity; Medtronic), and everolimus-eluting stent (EES) (Xience V, Xience Prime; Abbott Vascular, Santa Clara, California, USA or Promus; Boston Scientific). The repeated PCI procedures were divided into three groups: POBA (used only plain balloon; neither cutting balloon nor drug-eluting balloon), the use of the same type of DES [a homogeneous drug-eluting stent (HOMO-DES)], or the use of a different type of DES [a heterogeneous drug-eluting stent (HETERO-DES)]. The HOMO-DES procedure included exactly the same specific DES type as the first one (e.g. SES for SES ISR, etc.). The HETERO-DES procedure included switching not only the stent's drug coating but also the generation of the stent (e.g. EES for PES ISR, EES for E-ZES ISR, etc.). All patients received intravenous heparin (140 U/kg of body weight) during the procedure. The procedure was considered to be successful when a residual stenosis of less than 30% and a thrombolysis in myocardial infarction flow grade 3 were achieved in the treated vessel using the assigned stent. β-Blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were administered when considered necessary by the attending physician.

Exclusion criteria

We excluded patients who had already undergone repeated PCI for the same ISR lesion; had malignancies, or other comorbid conditions with a life expectancy of less than 12 months; had a known allergy to the study medication (ticlopidine, clopidogrel, or aspirin); or were fertile women.

Classification of the pattern of drug-eluting stent in-stent restenosis

The pattern of DES ISR before PCI was categorized into four groups according to the classifications described previously by Mehran *et al.* [21] Further, we divided these four restenosis into two groups, the focal group (Type I lesions) and the nonfocal group (Type II, III, and IV lesions), on the basis of their angiographic restenosis morphology.

Clinical follow-up

Major adverse cardiac events (MACE) included all-cause death; nonfetal acute coronary syndrome including stent thrombosis; admission for recurrent angina pectoris; and target lesion revascularization (TLR). Acute coronary syndrome was considered in cases where symptoms of prolonged myocardial ischemia and/or new significant ST-segment–T wave changes and/or the troponin I level were elevated. Stent thrombosis was defined by angiographic evidence of partial or total stent occlusion, with the presence of a thrombus on the basis of the Academic Research Consortium's stent thrombosis definition [22]. TLR was defined as revascularization driven by more than 70% diameter stenosis by visual estimation within the stent or within 5 mm of the proximal or distal border of the stent edge and the patients naturally had ischemic symptoms and/or objective ischemic findings. Clinical follow-up was obtained from review of medical records and/or telephone interviews.

Statistical analyses

Continuous variables are presented as mean ± SD or medians and categorical variables are presented as frequency (%). Data analyses were carried out according to a pre-established plan. Differences in proportions were tested using Pearson's χ^2-test or Fisher's exact test (whenever an expected cell value was <5) for categorical data; differences in the location pattern of continuous variables were tested using analysis of variance. If we noted a statistically significant difference among the three groups tested using analysis of variance, we applied the Tukey–Kramer test for each group. Multivariate regression analysis was carried out to evaluate the TLR risk factors. Event-free rate curves were assessed using the Kaplan–Meier method and compared using the log-rank test. A P-value of less than 0.05 was considered statistically significant. The JMP version 9 software (SAS Institute Inc., Cary, North Carolina, USA) was used for all analyses.

Table 1 Patient baseline and angiographic characteristics

	POBA (38 lesions) [*n* (%)]	HOMO (38 lesions) [*n* (%)]	HETERO (115 lesions) [*n* (%)]	*P*-value
Age (mean ± SD) (years)	72.0 ± 6.9	71.0 ± 7.6	69.7 ± 7.5	0.20
Men	26 (68)	26 (68)	80 (70)	0.99
Diabetes mellitus	23 (61)	24 (63)	71 (62)	0.97
Hypertension	31 (82)	27 (71)	84 (73)	0.51
Hyperlipidemia	30 (79)	27 (72)	81 (70)	0.59
Hemodialysis	2 (5)	3 (8)	10 (9)	0.79
Previous CABG	3 (8)	2 (1)	1 (1)	0.07
Previous AMI	16 (42)	16 (42)	53 (46)	0.86
Target vessel				0.64
LMCA	2 (5)	2 (6)	2 (2)	0.39
LAD	20 (53)	21 (55)	57 (50)	0.82
LCX	9 (24)	5 (13)	23 (20)	0.49
RCA	7 (18)	10 (26)	33 (28)	0.46
ISR pattern[a]				0.12
Type I (focal)	22 (58)	29 (77)	85 (74)	0.07
Type II (diffuse)	12 (31)	2 (5)	21 (18)	< 0.01
Type III (proliferative)	1 (3)	5 (13)	6 (5)	0.10
Type IV (occlusive)	3 (8)	2 (5)	3 (3)	0.34

AMI, acute myocardial infarction; CABG, coronary artery graft bypass; HETERO, implantation of a different type of drug-eluting stent (heterogeneous); HOMO, implantation of the same type of drug-eluting stent (homogeneous); ISR, in-stent restenosis; LAD, left anterior descending artery; LCX, left circumflex artery; LMCA, left main coronary artery; POBA, plain old balloon angioplasty; RCA, right coronary artery.
[a]According to the classification of Mehran *et al.* [21].

Results

Patient background

The patient baseline demographic, clinical, and angiographic characteristics are shown in Table 1 and the procedural characteristics are shown in Table 2. The baseline clinical characteristics were not significantly different among the three groups. Of the 191 lesions analyzed, 71.2% ($n = 136$) were focal (Type I) and 28.8% ($n = 55$) were nonfocal. Of the nonfocal lesions, 18.3% ($n = 35$) were diffuse (Type II), 6.3% ($n = 12$) were proliferative (Type III), and 4.2% ($n = 8$) were totally occluded (Type IV). According to the ISR pattern, 'focal' lesions tended to be less in the POBA group compared with the other two DES groups; however, there were no significant differences among the three groups ($P = 0.12$). Table 2 also shows that the patients with POBA compared with those with DESs showed a trend toward a smaller balloon size and a higher inflation pressure.

Angiographic results

The incidence of TLR was 42.1% (16/38), 15.8% (6/38), and 16.5% (19/115) in the POBA, HOMO-DES, and HETERO-DES groups (POBA vs. HOMO, HETERO-DES; $P = 0.002$, respectively). However, there were no significant differences between the HOMO and the HETERO groups. The incidence of TLR classified according to the pattern of DES ISR before PCI is also shown (Fig. 1). The TLR rate was 17% (20/121) in Type I lesions, 44% (12/27) in Type II lesions, 60% (6/10) in Type III lesions, and 50% (3/6) in Type IV lesions. On the basis of the group types, the TLR rate was 17% (20/121) in the focal group and 49% (21/43) in the nonfocal group ($P < 0.001$).

Switching between generations of drug-eluting stents

The incidence of TLR in patients who were switched from a first-generation DES to a first-generation DES was 16% (8/50). Similarly, switching from a first-generation DES to a second-generation DES resulted in a TLR incidence of 22% (11/49); switching from a second-generation DES to a first-generation DES resulted in a TLR incidence of 22% (2/9); and switching from a second-generation DES to a second-generation DES resulted in a TLR incidence of 17% (4/23). There were no significant differences associated with switching the generation of the DES used ($P = 0.86$) (Fig. 2).

Multivariate analysis

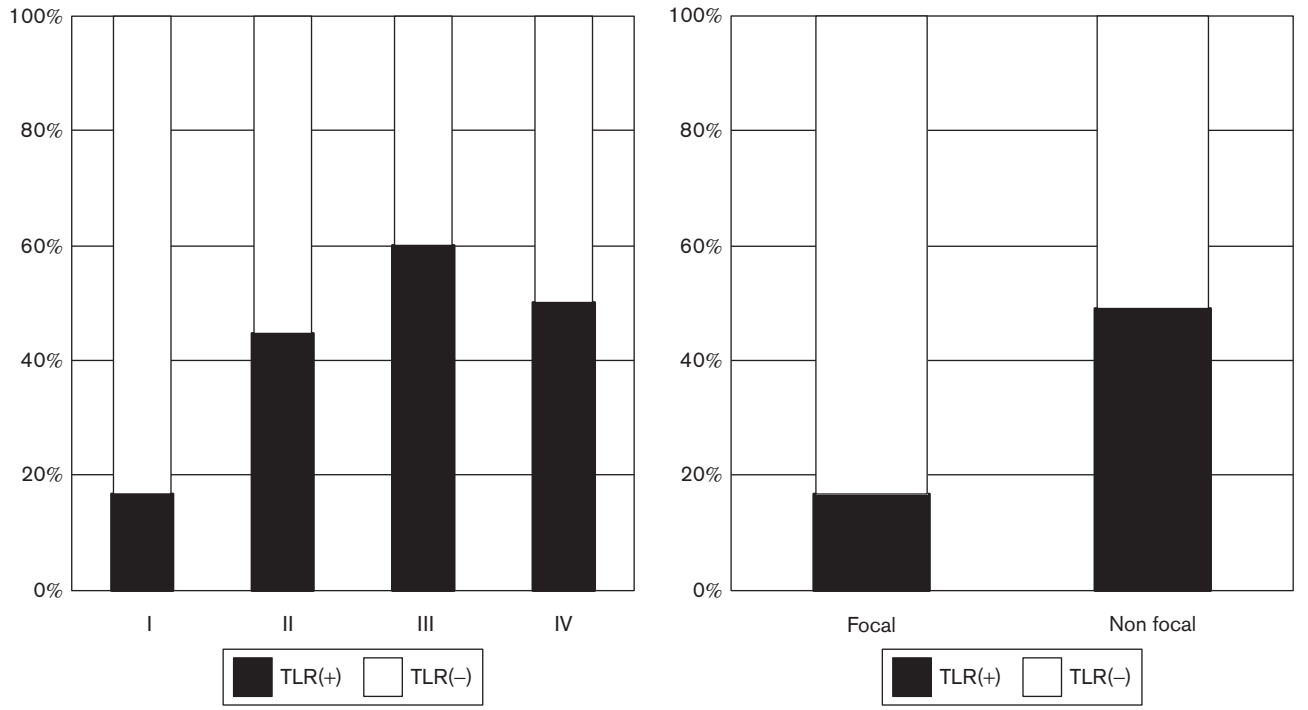
We introduced sex, hypertension, diabetes mellitus, hyperlipidemia, hemodialysis, nonfocal ISR, previous AMI, previous coronary artery bypass graft, POBA, stent

Table 2 Procedural characteristics

	POBA (38 lesions)	HOMO (38 lesions)	HETERO (115 lesions)	*P*-value
Stent generation [*n* (%)]				
First→first	0	22 (59)	32 (28)	N/A
First→second	0	0	59 (51)	N/A
Second→first	0	0	9 (8)	N/A
Second→second	0	16 (41)	15 (13)	N/A
Device details (mean ± SD)				
Prestent diameter (mm)	2.87 ± 0.32	2.9 ± 0.32	3.01 ± 0.38	0.10
Prestent length (mm)	23.7 ± 7.2	23.8 ± 8.3	23.2 ± 6.9	0.86
Predevice maximum inflation pressure (atm)	15.4 ± 3.8	15.0 ± 3.7	15.5 ± 3.4	0.78
PCI-stent or balloon diameter (mm)	2.89 ± 0.46*	3.07 ± 0.38	3.09 ± 0.38*	0.03
PCI-stent or balloon length (mm)	13.5 ± 3.2	16.2 ± 7.2	15.5 ± 6.9	0.16
PCI device maximum inflation pressure (atm)	19.2 ± 3.7‡	17.9 ± 3.6†	16.0 ± 3.8†,‡	< 0.001

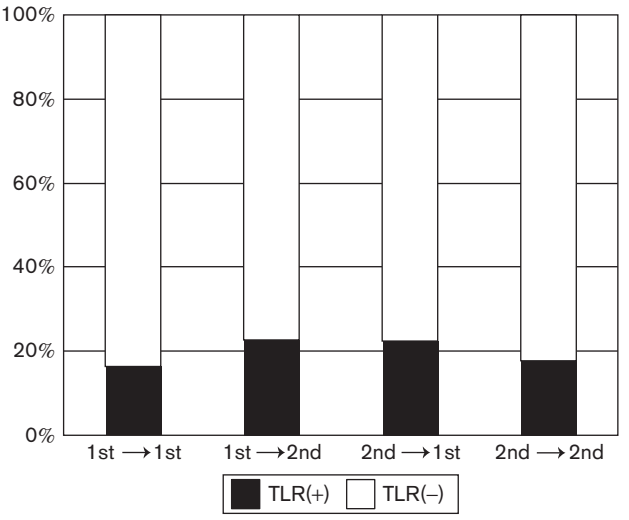
HETERO, implantation of a different type of drug-eluting stent (heterogeneous); HOMO, implantation of the same type of drug-eluting stent (homogeneous); PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty.
*$P = 0.02$.
†$P = 0.02$.
‡$P < 0.001$ (Tukey–Kramer test).

Fig. 1



The predominant target lesion revascularization (TLR) pattern, according to Mehran's classification, was focal (Type I) and this pattern is associated with a lower incidence of TLR. $P < 0.001$.

Fig. 2



Impact of drug-eluting stent generation on target lesion revascularization (TLR). Switching the generation of drug-eluting stent did not contribute toward a reduction in TLR. No statistical differences were noted in the patients in whom the generation of drug-eluting stents was switched. $P = 0.86$.

length and diameter, maximum balloon pressure, estimated glomerular filtration rate, and low-density lipoprotein level into a multivariable model to identify the predictors of the need for TLR. The parameters that independently predicted the need for TLR, after ISR treatment, were ISR pattern, according to the 'nonfocal' angiographic classification [odds ratio (OR), 3.05; $P = 0.02$]; previous AMI (OR, 2.58; $P = 0.03$); previous coronary artery bypass graft (OR, 13.1; $P = 0.05$); POBA (OR, 8.37; $P < 0.001$); diabetes mellitus (OR, 3.18; $P = 0.02$); and the need for hemodialysis (OR, 7.26; $P < 0.01$) (Table 3). Hyperlipidemia, estimated glomerular filtration rate, low-density lipoprotein level, stent/balloon length and diameter, target vessel, and maximum stent or balloon pressure were eliminated in this model.

Table 3 Predictors of target lesion revascularization

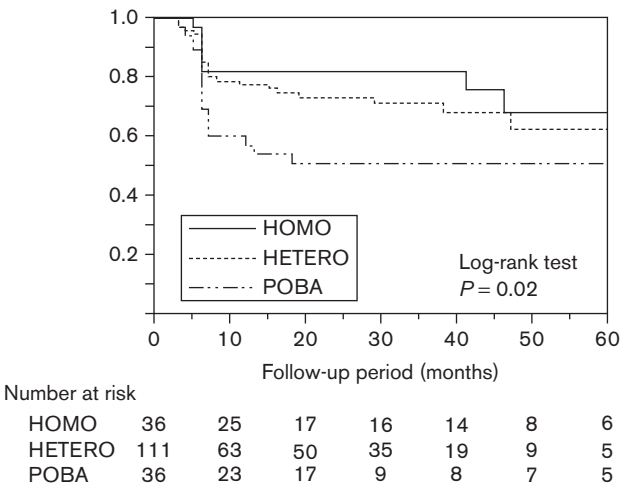
	OR (95% CI)	*P*-value
Diabetes mellitus	3.18 (1.27–9.23)	0.02
Hemodialysis	7.26 (1.80–32.9)	< 0.01
Nonfocal (ISR pattern)[a]	3.05 (1.23–7.65)	0.02
Previous AMI	2.58 (1.09–6.47)	0.03
Previous CABG	13.1 (1.04–182.7)	0.05
POBA	8.37 (3.08–24.9)	< 0.001

AMI, acute myocardial infarction; CABG, coronary artery graft bypass; CI, confidence interval; ISR, in-stent restenosis; OR, odds ratio; POBA, plain old balloon angioplasty.
[a]Nonfocal: Type II, III, and IV according to the classification of Mehran *et al.* [21].

Clinical outcomes

The Kaplan–Meier curves for cumulative freedom from MACE are shown in Fig. 3. The POBA group had

Fig. 3



Major adverse cardiac event (MACE)-free survival curve. The repeated use of drug-eluting stent may be more effective and safe than POBA for the prevention of recurrent restenosis. MACE included death, acute myocardial infarction, admission for recurrent angina pectoris, and target lesion revascularization. The POBA group showed the highest MACE rates of the three groups. HETERO, implantation of a different type of drug-eluting stent (heterogeneous); HOMO, implantation of the same type of drug-eluting stent (homogeneous); POBA, plain old balloon angioplasty.

a significantly lower event-free rate compared with the other two DES groups ($P=0.02$). Rates of each component of freedom from MACE composited endpoints at 6 months and 5 years (POBA: 70, 50%, HOMO-DES: 82, 68%; HETERO-DES: 85, 63%, respectively). During the observation period, stent thrombosis occurred in one patient in the POBA group, one patient in the HOMO group, and two patients in the HETERO group ($P=0.91$). There were no statistically significant differences in the three groups.

Discussion

DESs are considered to be very important devices in the PCI era. However, the incidence of TLR following DES implantation has not approached zero. In part, this is because interventionalists are performing PCIs with DESs in increasingly difficult cases, involving very complex lesions, and expecting powerful suppression of neointimal growth following DES implantation. Moreover, the relatively low frequency of DES ISR events increases the difficulty of fully investigating these events. Thus, many studies have been carried out or are ongoing to determine the mechanism, incidence, predictors, and optimal treatment in such cases [23–26]. The proposed mechanisms for the development of this condition include mechanical factors, such as underexpansion or overexpansion of the stent, stent fracture, nonuniform strut distribution, or stent malapposition. Moreover, there may also be drug-specific factors, such as nonuniform drug deposition, polymer peeling during stent delivery, localized hypersensitivity, and drug resistance [27]. Sirolimus (rapamycin), for example, inhibits the function of the mammalian target of rapamycin (mTOR) and suppresses smooth muscle cell migration and proliferation by arresting cells in the G1 phase or, potentially, by inducing cell apoptosis [17,18]. However, recent data indicate that genetic mutations or compensatory changes also influence mTOR sensitivity, thus conferring rapamycin resistance [19]. Laboratory investigations have also shown a variety of resistance mechanisms for paclitaxel [20]. The rationale for using a different DES in cases of DES ISR is based on the different mechanisms of action of their active pharmacologic agents. Therefore, the deployment of a different DES might be more effective than retreatment with a stent containing the same drug. A few studies have investigated the use of the same or different DESs to treat DES ISR [28–30]. Mishkel *et al.* [31] reported that treatment with a different DES tended to result in more favorable 12-month outcomes compared with treatment with the same DES. In general, these studies have involved only SES and PES; to our knowledge, reports on the use of ZES or EES for treating DES ISR have not been published. In the present study, ISR treatment involving a heterogeneous DES or switching between generations of devices was not shown to be more effective than the use of a homogeneous DES. These findings may be attributed to the small sample size; moreover, we used DESs to treat off-label lesion indications, including bifurcations of the left main coronary artery and AMI-induced lesions. Nevertheless, the repeated use of DESs yielded results that were better than those with the use of POBA in patients with DES ISR. Although POBA treatment showed a high incidence of revascularization, we may expect favorable results from the use of a drug-eluting balloon. The use of drug-eluting balloons also yielded excellent results in a previous case of BMS and DES restenosis [32]. A precise understanding of the mechanism and related factors (biological, mechanical, and technical) involved in DES restenosis is required to design a tailor-made approach for the treatment of DES ISR. This is especially true, given that a diffuse pattern of intimal tissue growth occurs with the use of these various modern types of stents, and is associated with a high incidence of repeated restenosis, as evidenced by the current study.

Study limitations

This study has certain limitations. First, its design involved a nonrandomized, single-center, historical prospective cohort, with a relatively small population. Considering the low power of this study, specific clinical questions remain unresolved. In brief, we were unable to clarify which type of stent should be used first and which type of stent should be used after the restenosis. Therefore, additional randomized studies are warranted

to elucidate the optimal treatment of DES ISR. Second, especially in the POBA group, operators subconsciously tended to choose 'POBA' as a strategy in cases where insufficient expansion of stent struts was confirmed by intravascular ultrasonography or where long complex restenotic lesions were confirmed by CAG; thus, some bias may have been associated with this group. Third, we performed the follow-up CAG 6 months after the procedure. However, the optimal time for observing DES-associated restenotic changes remains unknown. Some authors have reported the occurrence of late restenosis following the implantation of first-generation DESs [33,34]. Moreover, no reports have described the association between late restenosis and second-generation DESs. In the present study, we also observed that TLR was required after the 6-month follow-up in certain cases.

Conclusion

For patients with DES ISR, a strategy involving repeated DES was found to be superior to POBA for the prevention of recurrent restenosis. However, switching DES type did not contribute toward a reduction in TLR. Indeed, the present results suggest that repeated DES implantations, irrespective of whether or not they involve the same generation of stent or the same drug, may be more effective and feasible than POBA for patients with DES ISR.

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Conflicts of interest

There are no conflicts of interest.

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