Mehran in-stent restenosis classification adapted for coronary bifurcations: the impact on 4-year follow-up from randomized clinical studies POLBOS I and II

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Introduction

Percutaneous coronary interventions (PCI) with stent deployment are the most widely performed procedures in the therapy of symptomatic coronary artery disease (CAD). In the last three decades, PCI with stent deployment has changed the practice in cardiology. Drug-eluting stents (DES) significantly reduced in-stent restenosis (ISR) rates – one of the key limitations of bare metal stents. In consequence, DES were rapidly and widely accepted, which allowed more complex coronary interventions, including bifurcations, to be performed. Nevertheless, ISR has remained a troublesome late stent complication [1, 2].

Multiple classification systems addressed the problem of ISR severity. The Mehran classification is a morphologic system which divides ISR lesions into four patterns: from focal pattern I when ISR is ≤ 10 mm in length within the stent to pattern IV when the ISR is the cause of vessel occlusion [3].

Aim

The aim of our study was to propose a modified Mehran restenosis classification adapted to bifurcation lesions and preliminarily assess its value in the 4-year follow-up on data from two randomized studies, POLBOS I and POLBOS II, that compared dedicated bifurcation BiOSS stents with regular drug-eluting stents (rDES) [4–6].

Material and methods

POLBOS I and POLBOS II were international, multicenter, randomized, open-label, controlled studies described previously [4, 6]. Briefly, the inclusion criteria were: stable CAD or non-ST-segment elevation acute coronary syndrome (NSTE-ACS), age ≥ 18 years, *de novo* coronary bifurcation lesion, main vessel (MV) diameter ≥ 2.5 mm, and side branch (SB) diameter ≥ 2.0 mm on visual estimation. The Institutional Review Board of each participating center approved the study protocol (ClinicalTrials.gov Identifier: POLBOS I – NCT02192840, POLBOS II – NCT02198300).

After providing written informed consent, patients were randomly assigned to one of two treatment strategies: BiOSS Expert (in POLBOS I)/BiOSS LIM (in POLBOS II) stent implantation or rDES implantation [7–9]. Provisional T-stenting was the default strategy. The stent nominal diameter was chosen according to the distal reference, and after stent deployment, the proximal part of the stent was optimized, if needed, with proximal optimization technique (POT) to obtain the proper apposition.

Clinical follow-up was performed by telephone 1, 6, 12, 24, 36 and 48 months after the procedure. Adverse events were monitored throughout the study period. Follow-up coronary angiography was mandatory at 12 months unless clinically indicated earlier.

The primary endpoint was the cumulative rate of major adverse cardiovascular events (MACE) consisting of cardiac death, myocardial infarction (MI), and target lesion revascularization (TLR). Secondary endpoints included cardiac death, all-cause death, MI, TLR, target vessel revascularization (TVR), stent thrombosis (ST), and device success. Cardiac death included death resulting from an acute MI, sudden cardiac death, death due to

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heart failure, and death due to cardiac procedures. All deaths were deemed cardiac unless proven otherwise. Myocardial infarction was defined according to the third universal definition [10].

Bearing in mind the different approach for bifurcation stenting (nominal stent diameter chosen on the basis of distal reference diameter and then optimization of the proximal part of the stent with POT and final kissing balloons technique (FKB)) we proposed a modified Mehran restenosis classification adapted for coronary bifurcation lesions (Figure 1). We divided the stent according to the parts of the bifurcation, i.e. the MV and main branch (MB), and additionally we took into consideration the SB since it is an inseparable part of the bifurcation complex. In each pattern (I–IV) we introduced subgroups to localize the restenosis (in MV, in MB, in SB, or in combina-

Modified Mehran's classification adapted for restenosis in bifurcation lesions

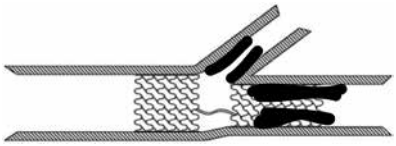
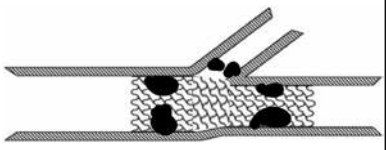
Type of restenosis	BiOSS (*n* = 24)	rDES (*n* = 17)
I (focal restenosis, < 10 mm in stent):	**14 (58.3%)**	**9 (52.9%)**
A (in MV)	4 (28.6%)	2 (11.8%)
B (in MB)	2 (14.3%)	1 (5.9%)
C (in SB)	5 (20.8%)	3 (17.7%)
D (in SB and MB)	1 (4.2%)	2 (11.8%)
E (in SB and MV or in all parts)	2 (14.3%)	1 (5.9%)
II (> 10 mm within the stent):	**5 (20.8%)**	**5 (29.4%)**
A (in MV)	1 (4.2%)	1 (5.9%)
B (in MB)	1 (4.2%)	0
C (in SB)	0	0
D (in SB and MB)	2 (14.3%)	2 (11.8%)
E (in SB and MV or in all parts)	1 (4.2%)	2 (11.8%)
III (> 10 mm + outside the stent):	**2 (8.3%)**	**2 (11.8%)**
A (in MV)	1 (4.2%)	1 (5.9%)
B (in MB)	0	0
C (in SB)	0	0
D (in SB and MB)	1 (4.2%)	1 (5.9%)
E (in SB and MV or in all parts)	0	0
IV (total occlusion):	**3 (12.5%)**	**1 (5.9%)**
A (in MV)	0	0
B (in MB)	1 (4.2%)	1 (5.9%)
C (in SB)	1 (4.2%)	0
D (in MB and SB)	1 (4.2%)	0
Exemplary cases:	 BiOSS: ISR type III D	 rDES: ISR type I E

Figure 1. Modified Mehran restenosis classification. In each pattern (I–IV) we introduced subgroups to localize the restenosis (in MV-MB, in SB, or in both, respectively). Point IIC is optional depending on the SB stenting, in other cases SB restenosis characterizes the lesion irrespectively of whether it was stented or not since SB is an inseparable part of the bifurcation complex

MV – main vessel, MB – main branch, SB – side branch.

tions). The MV was defined as the proximal part of the bifurcation up to the take-off of the SB, and the MB was defined as the distal part of the bifurcation below the take-off of the SB.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. Categorical data were presented as numbers (%). Continuous variables were compared using an unpaired two-sided Student *t*-test, and categorical data using the χ^2 test or Fisher's exact test, as appropriate. If the distribution was not normal on the Shapiro-Wilk test, the Wilcoxon signed-rank and Mann-Whitney *U*-tests were used. *P*-values of < 0.05 were considered statistically significant. The significance level was set at 0.05. Statistical analyses were performed using R 3.0.2 for OS (R Foundation, Vienna, Austria).

Results

Our population of 445 patients, with 222 patients in the BiOSS group and 223 patients in the rDES group, was analyzed. In the BiOSS group there were 24 (10.8%) cases of restenosis and in the rDES group 17 (7.6%) cases at 12-month follow-up (the rate of angiographic control was 90.3%). Baseline clinical and procedural characteristics of patients with restenosis are presented in Table I. In the rDES group in patients with restenosis there was a higher rate of diabetes type 2 (33% vs. 52.9%, $p < 0.05$)

Table I. Baseline population characteristics in the whole population

Parameter	BiOSS group		rDES group	
	No restenosis (*n* = 198)	Restenosis (*n* = 24)	No restenosis (*n* = 206)	Restenosis (*n* = 17)
Baseline clinical characteristics:				
Age [years]	66.6 ±9.7	65.2 ±12.6	66.5 ±9.1	65.6 ±9.5
Women	57 (28.8%)	5 (20.8%)	61 (29.6%)	3 (17.6%)
Hypertension	158 (79.8%)	22 (91.7%)	158 (76.7%)	13 (76.5%)**
Hypercholesterolemia	143 (72.2%)	17 (70.8%)	136 (66%)	14 (82.4%)*
Diabetes type 2	82 (41.4%)	8 (33.3%)	63 (30.6%)	9 (52.9%)*,**
Prior myocardial infarction	85 (42.9%)	14 (58.3%)*	82 (39.8%)	8 (47.1%)
Prior PCI	101 (51%)	11 (45.8%)	109 (52.9%)	6 (35.3%)*
Coronary artery bypass graft	17 (8.6%)	4 (16.7%)	19 (9.2%)	3 (17.6%)
Chronic kidney disease	22 (11.1%)	1 (4.2%)	16 (7.8%)	3 (17.6%)
History of smoking	44 (22.2%)	3 (12.5%)	50 (24.3%)	7 (41.2%)*,**
Clinical indication for PCI:				
Planned PCI	167 (84.3%)	19 (79.2%)	176 (85.4%)	10 (58.8%)*,**
UA/NSTEMI	31 (15.7%)	5 (20.8%)	30 (14.6%)	7 (41.2%)*,**
True bifurcation	167 (84.3%)	11 (45.8%)*	176 (85.4%)	9 (52.9%)*
Left main bifurcation	57 (28.8%)	5 (20.8%)	51 (24.8%)	6 (35.3%)
Procedural characteristics:				
Main vessel predilatation	117 (59.1%)	20 (83.3%)*	145 (70.4%)	14 (82.4%)
Side branch predilatation	67 (33.8%)	7 (29.2%)	57 (27.7%)	8 (47.1%)*,**
Olimus-eluting stents	88 (44.4%)	14 (58.3%)	148 (71.8%)	7 (41.2%)*,**
Paclitaxel-eluting stents	110 (55.6%)	10 (41.7%)	58 (28.2%)	10 (58.8%)*,**
Proximal optimization technique	81 (40.9%)	2 (8.3%)*	152 (73.8%)	1 (5.9%)*
Final kissing balloon	65 (32.8%)	6 (25%)	101 (49%)	9 (52.9%)**
Additional stent in side branch	17 (8.6%)	5 (20.8%)	7 (3.4%)	8 (47.1%)*,**

*PCI – percutaneous coronary intervention, UA/NSTEMI – unstable angina/non-ST-elevation myocardial infarction; *p < 0.05 no restenosis vs restenosis in BiOSS or rDES group; **p < 0.05 restenosis between BiOSS and rDES groups.*

and a history of smoking (12.5% vs. 41.2%, $p < 0.05$) and a lower rate of hypertension (91.7% vs. 76.5%, $p < 0.05$) compared with the BiOSS group. In the rDES group in patients with restenosis there was a higher rate of SB predilatation (29.2% vs. 47.2%, $p < 0.05$), final kissing balloon technique (25% vs. 52.9%, $p < 0.05$), and additional stent in the SB (20.8% vs. 47.1%, $p < 0.05$) compared with the BiOSS group.

The rates of restenosis in the BiOSS group in the MV, MB and SB were 41.7% ($n = 10$), 37.5% ($n = 9$) and 54.2% ($n = 13$), respectively, whereas rates of restenosis in the rDES group in the MV, MB and SB were 35.3% ($n = 6$), 41.2% ($n = 7$) and 64.7% ($n = 11$), respectively. Type I was observed in 58.3% and 52.9% in BiOSS and rDES groups, respectively, whereas the other types were less frequent (type II: 20.8% vs. 29.4%; type III: 8.3% vs. 11.8%; type IV: 12.5% vs. 5.9%). In the BiOSS group most commonly restenosis type IA (focal, in MV) was observed (28.6%), whereas in rDES restenosis type IC (focal, in SB) was most common, with an incidence of 17.7% (Figure 1).

In the BiOSS group 2 (8.3%) restenosis cases were treated with CABG, 4 (16.7%) with plain old ballon angioplasty/drug-eluting ballon (POBA/DEB) and 18 (75%) with another DES implantation. In the rDES group 1 (5.9%) restenosis case was treated with CABG, 4 (23.5%) with POBA/DEB and 12 (70.6%) with another DES implantation.

At 12 months after the first ISR the death rates were 0, 0, 25% ($n = 1$) and 0 for types I, II, III, IV, respectively; the MI rates were 4.3% ($n = 1$), 0, 0 and 0, whereas the TLR rates were 17.4% ($n = 4$), 20% ($n = 2$), 25% ($n = 1$) and 50% ($n = 2$). There were no statistical differences between BiOSS and rDES.

At 36 months after the first ISR the death rates were 4.3% ($n = 1$), 0, 25% ($n = 1$) and 0 for types I, II, III, IV, respectively; the MI rates were 8.6% ($n = 2$), 10% ($n = 1$), 0 and 0, whereas the TLR rates were 26.1% ($n = 6$), 30% ($n = 3$), 25% ($n = 1$) and 50% ($n = 2$). There were no statistical differences between BiOSS and rDES.

Discussion

In-stent restenosis manifests in different angiographic patterns. We have proposed a classification which takes into account not only lesion length but also the location of the neointimal proliferation relative to the initially implanted stent in the bifurcation complex as well as to the stages of the PCI reflecting the proper stent apposition. There were no significant differences between BiOSS stents and rDES restenosis profile.

In the original Mehran classification 12-month clinical event rates were evenly high, without significant differences between groups regarding death or MI. However, a significant increase in TLR with increasing levels of ISR classification (class I, 19%; class II, 35%; class III, 50%; and class IV, 83%; $p < 0.0001$) was observed. This was caused by significantly increasing rates of PCI (15%, 26%, 36%, and 67% in classes I to IV, respectively; $p < 0.0001$) as well as CABG (4%, 8%, 14%, and 17% in classes I to IV, respectively; $p < 0.0001$) [3]. In our paper we obtained lower TLR rates. Although we treated bifurcation lesions characterized by higher failure rates, we used drug-eluting stents (mainly second generation), which perform better than bare metal stents available in 1999. Moreover, the procedure technique is quite different with FKB performed quite often and mandatory POT. Also, opposite to Mehran's initial paper we did not observe a very high rate of subsequent revascularizations after interventional therapy (ISR treatment) with currently available treatment modalities in patients presenting with higher ISR classes. Similar results were obtained both in the RIBS and RIBS II trials [11, 12].

In further studies, it would be of interest to verify whether the performance of the PCI with bifurcation lesions according to the European Bifurcation Club, especially performing POT or not, has an influence on the restenosis profile and the nature of such change [13].

Conclusions

In-stent restenosis presents with different angiographic patterns that might provide helpful prognostic information. There were no significant differences between the BiOSS stent and rDES restenosis profile in short- or long-term follow-up.

Conflict of interest

Robert J. Gil is a Balton consultant. Other authors declare no conflict of interest.

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