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Comparison between balloon angioplasty and additional coronary stent implantation for the treatment of drug-eluting stent restenosis: 18-month clinical outcomes

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Objective **To evaluate the long-term outcomes after different modalities of treatment of drug-eluting stent (DES) in-stent restenosis (ISR) in a 'real world' setting.**

Methods **Actually, few and conflicting data are available about the management of in-stent restenosis (ISR) after DES implantation. In our 'real world' registry 1082 consecutive patients who received a DES implantation were included. At 9-month angiographic follow-up, 93 patients presented a DES ISR that was treated with 'homo-DES' (HMD) ($N = 27$), 'hetero-DES' (HTD) ($N = 19$) and conventional balloon angioplasty (POBA) ($N = 47$). We evaluated the clinical outcomes in terms of major adverse cardiac event (MACE) (death, myocardial infarction and target vessel revascularization) at 18 months.**

Results **There was no difference for clinical and angiographic characteristics between the three groups, except for the presence of silent ischaemia as clinical presentation (7.7 HMD vs. 2.2% POBA; $P = 0.0001$). No late stent thrombosis was found. At 18-month clinical follow-up patients treated with HMD, HTD and POBA presented a rate of MACE of 10.2, 0 and 8.7%, respectively ($P =$ NS). Kaplan–Meier survival probability showed that HTD and POBA treatment tended to have more favourable outcomes at 18 months than the HMD treatment.**

Conclusion **In our registry, POBA seems to be as effective as other DES implantations in cases of DES ISR, especially in cases of focal type (Mehran classification IA, IC), in terms of long-term outcomes. *J Cardiovasc Med* 10:469–473 © 2009 Italian Federation of Cardiology.**

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Introduction

Drug-eluting stents (DES) have significantly reduced the incidence of binary restenosis and repeat coronary revascularization as compared with bare-metal stents (BMS) [1–7]. Nevertheless, in-stent restenosis (ISR) remains the major limitation to coronary stenting [8–10]. Conventional percutaneous coronary balloon angioplasty (POBA) remains the most commonly used approach to treat ISR [11–15]. The so called 'sandwich stenting' technique (stent within a stent) using an additional DES, represents an innovative therapeutic breakthrough, but larger studies are needed to assess if their systematic use is justified in all patients with DES ISR.

A recent study showed that treatment of ISR using POBA compared with another DES implantation, eluted with the same [homo-DES implantation (HMD)] or another type of drug [hetero-DES implantation (HTD)], is associated with an higher rate of major adverse cardiac events (MACE), including death, myocardial infarction (MI) and target vessel revascularization (TVR) [16].

We sought to analyse long-term clinical outcomes among non-selected patients who underwent DES implantation and developed DES ISR subsequently treated with POBA, HMD or HTD implantation.

Methods

We included in a 'real-world' registry all consecutive patients who were implanted with at least one DES in at least one coronary vessel. An angiographic follow-up was routinely scheduled at 9 months.

ISR was defined as at least 50% diameter stenosis narrowing of the lumen diameter in the target lesion within the first implanted DES at angiogram. All treated lesions were within the previous implanted DES. Patients who developed restenosis at 5 mm of its edges, according to

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Meheran morphology restenosis classification [17], were excluded from our analysis.

During the procedure, intravenous unfractioned heparin was administered to maintain the activated clotting time (ACT) at least 250 s. Periprocedural glycoprotein (GP) IIb/IIIa receptor inhibitors were used at the operators' discretion. At the moment of in-stent restenosis percutaneous intervention (PCI) a loading dose of clopidogrel was not administered because all patients were in dual antiplatelet therapy. Dual antiplatelet therapy was recommended at least 12 months after new DES placement or POBA intended as conventional balloon angioplasty; in this group we did not use any cutting balloon. The choice of DES implanted was at the operators' discretion. The present investigation conforms to the principles outlined in the Declaration of Helsinki. The local ethical committee approved the study and all patients signed informed consent.

Follow-up

After ISR treatment a clinical follow-up was performed at 18 months by interview and non-invasive check-up (tread mill test and transthoracic echocardiography) for all patients.

Clinical MACE was defined as a composite of death, MI and TVR. Myocardial infarction was defined as the presence of prolonged chest pain (>30 min) followed by the development of new pathological Q waves lasting at least 0.4 s in at least two leads, with postprocedural creatine kinase (CK) levels more than two times the upper normal limit with positive CK-MB. Target vessel revascularization was defined as any clinical driven percutaneous revascularization or bypass in the target lesion or any segment of the epicardial coronary artery containing the target lesion.

Statistical analysis

Discrete variables are reported as percentages and continuous variables as mean ± SD. Chi-square and Fisher exact tests were used to compare discrete variables and Student *t* tests for continuous variables. Actuarial 18-month rates of MACE were examined by the Kaplan–Meier survival probability. Cox proportional hazard modelling was used to assess independent predictors of MACE at 18 months. Values $P < 0.05$ were considered statistically significant. Data were analysed with SPSS 11.0 for Windows (SPSS, Inc., Chicago, Illinois, USA).

Results

Patients ($N = 1082$) were treated with at least one DES on 1917 coronary lesions: 1122 with a paclitaxel-eluting stent (PES, TAXUS Express^2 Boston Scientific, Natick, Massachusetts, USA), 635 with a sirolimus-eluting stent (SES, Cypher, Cordis, Johnson & Johnson, New Brunswick, New Jersey, USA) and the remaining 160 with a tacrolimus-eluting stent (TES, JANUS CARBOSTENT,

Table 1 Clinical characteristics of each treatment group

Clinical variables	All ($N = 93$)	Homo-DES ($N = 27$)	Hetero-DES ($N = 19$)	POBA ($N = 47$)	*P* value
Age (years) (mean ± SD)	60.5 ± 10.3	58.1 ± 11.0	66.8 ± 9.5	61 ± 9.2	0.22
Men (%)	70.9	77.7	68.4	82.9	0.86
Diabetes (%)	26.9	7.4	47.3	25.5	0.07
NIDDM (%)	15.0	0	47.3	12.8	0.21
IDDM (%)	8.6	7.4	0	12.8	0.11
Hypertension (%)	62.4	77.7	78.9	63.9	0.41
Hypercholesterolaemia (%)	60.2	77.7	63.1	55.3	0.072
Current smoker (%)	50.5	77.7	47.3	48.9	0.093
Family history of CAD (%)	76.3	100	73.1	82.9	0.064
Prior MI (%)	18.3	37.0	10.5	17.0	0.056
Prior PCI (%)	13.9	29.6	21.0	19.2	0.36
Prior CABG (%)	7.5	7.4	10.5	4.2	0.84
STEMI at presentation (%)	17.2	22.2	10.5	17.0	0.79
LVEF (%) (mean ± SD)	48.9 ± 8.6	45.7 ± 11.3	47.7 ± 10.6	51.5 ± 13.1	0.09
Indication for repeat PCI					
Stable angina (%)	31.2	29.6	47.3	25.5	0.09
UA/NSTEMI (%)	33.3	48.1	47.3	17.0	0.07
STEMI (%)	4.3	7.4	0	4.2	0.21
Silent ischaemia (%)	31.2	7.4	10.5	51.0	<0.001
GP IIb/IIIa inhibitors (%)	19.3	23.4	28.3	15.2	0.07
Therapy at discharge					
Cardiospirin (%)	100	100	100	100	1
Clopidogrel (%)	100	100	100	100	1
Nitrates	100	100	100	100	1
Beta-blockers/Ca^{2+} channel blockers	86.3	85.4	87.7	85.4	0.91
ARBS/ACE-inhibitors	83.5	81.4	79.3	85.4	0.85
Statins	100	100	100	100	1

ACE, angiotensin-converting enzyme; ARBS, angiotensin II receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; GP, glycoprotein; Hetero-DES, drug-eluting stent implantation, eluted with the same drug; Homo-DES, drug-eluting stent implantation, eluted with the same drug; IDDM, insulin-dependent diabetes mellitus; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NIDDM, non-insulin-dependent diabetes mellitus; PCI, percutaneous intervention; POBA, conventional balloon angioplasty; STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction.

Table 2 Angiographic parameters in each treatment group

Angiographic parameters	All ($N=122$)	Homo-DES ($N=39$)	Hetero-DES ($N=26$)	POBA ($N=57$)	P value
Reference vessel diameter (mm) (mean ± SD)	2.9 ± 0.4	2.9 ± 0.3	2.8 ± 0.5	2.9 ± 0.5	0.83
Lesion length (mm) (mean ± SD)	18.5 ± 15.6	16.7 ± 7.7	15.1 ± 14	21.5 ± 19.1	0.52
Prestenosis (%) (mean ± SD)	80.5 ± 14.7	73.1 ± 27.2	74.3 ± 21.1	65.3 ± 28.6	0.89
Poststenosis (%) (mean ± SD)	3.0 ± 2.1	2.7 ± 4.9	2.2 ± 3.4	2.1 ± 2.8	0.26
Target vessel (%)					
Left anterior descending	46.7	61.5	53.8	35.1	0.17
Left circumflex artery	26.3	17.9	15.4	31.6	0.06
Right coronary artery	24.5	15.4	23.1	33.3	0.05
Ramus	1.6	0	7.7	0	0.08
Lesion morphology (%)					
Focal in-stent	59.8	64.1	34.6	68.4	0.11
Diffuse	28.7	25.6	50	21	0.04
Occlusion	11.5	10.3	15.4	10.6	0.88

Hetero-DES, drug-eluting stent implantation, eluted with the same drug; Homo-DES, drug-eluting stent implantation, eluted with the same drug; POBA, conventional balloon angioplasty.

Sorin Group, Brescia, Italia). Among the 831 (67.6%) patients who underwent the scheduled angiographic follow-up at 9 months, 93 (12.7%) developed ISR: 47 (50.5%) were treated with conventional balloon-only angioplasty, 27 (29%) received an HMD and the remaining 19 (20.5%) an HTD.

Clinical characteristics of the 93 patients who developed ISR and the 738 who did not present ISR at angiographic follow-up were similar (Table 1) except for the presence of current smokers (50.5 and 67.5% respectively, $P=0.0001$) and a history of prior myocardial infarction (18.3 vs. 33.7%, $P=0.0018$). There were no significant statistical differences among the three treatment groups (POBA, HMD and HTD) concerning clinical characteristics, except for the presence of non-insulin-dependent diabetes mellitus (0 in HMD group vs. 47.3% in HTD, $P=0.01$) and silent ischaemia as indication to perform a new procedure of revascularization at 9 months (7.4 in HMD vs. 51.0% in POBA group, $P=0.01$). Table 2 shows the angiographic and procedural characteristics in the three groups. In-stent restenosis lesion morphology, derived by Mehran classification, was focal in 59.8%, diffuse in 28.7% and total stent occlusion in 11.5% of overall ISR population.

No in-hospital adverse events, including death, acute stent thrombosis, myocardial infarction, or new revascularization occurred. Cox univariate analysis showed that age [HR 0.923 (CI 95% 0.864–0.986; $P=0.017$)], hypertension [HR 0.461 (CI 95% 0.124–1.717; $P=0.248$)], number of implanted stent [HR 1.435 (CI 95% 0.974–2.115; $P=0.068$)]; prior MI [HR 1.815 (CI 95% 0.454–7.258; $P=0.399$)]; left ventricular ejection fraction (LVEF) % [HR 1.026 (CI 95% 0.928–1.134; $P=0.622$)]; GP IIb/IIIa inhibitors [HR 7.761 (CI 95% 1.938–31.071; $P=0.004$)]; postprocedural rate of stenosis [HR 1.050 (CI 95% 0.978–1 0.127; $P=0.178$)] are independent predictors of MACE. At multivariate analysis, age [HR 1.235 (CI 95% 1.088–1.402; $P=0.012$)]; LVEF % [HR 1.168 (CI 95% 0.075–4.338; $P=0.037$)]; GP IIb/IIIa inhibitors [HR 6.301 (CI 95% 1.037–3.151; $P=0.076$)]; postprocedural rate of stenosis [HR 1.153 (CI 95% 0.060–5.682; $P=0.017$)] are independent predictors of MACE. Kaplan–Meier survival curve is shown in Fig. 1.

Follow-up events

The main duration of follow-up was 25.3 ± 7.5 months. At the time of follow-up dual antiplatelet therapy was suspended in all patients. Two patients (2.1%), both treated with HMD, presented a cardiac death 9 months after the procedure and six (6.4%) had a target lesion revascularization (two in the HMD and four in the POBA groups). Five patients were treated with a new percutaneous revascularization and one underwent coronary artery bypass graft (CABG). No cases of MI occurred among the three groups (Table 3). Patients in the HTD group did not present MACE during all the follow-up period. Finally, we showed that there is no difference between homo-DES, hetero-DES and POBA treatment.

Discussion

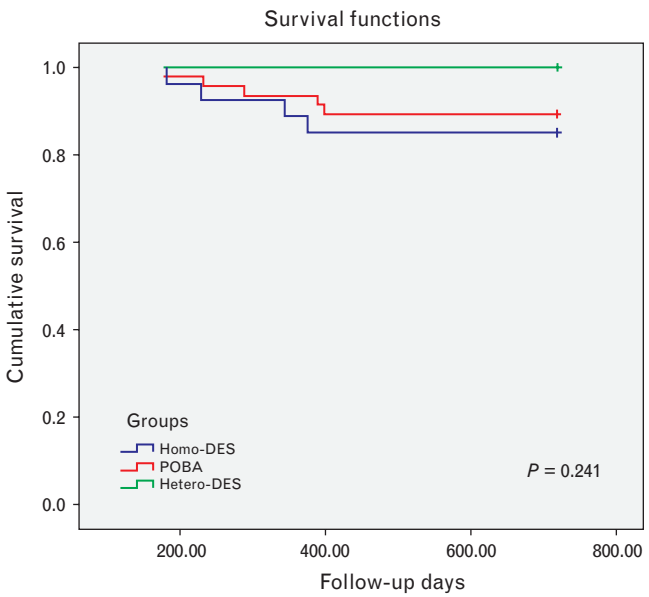
The major finding of this study is that, in case of DES ISR POBA treatment, homo-DES and hetero-DES do not showing differences with regard to death, MI and TVR at

Table 3 18-Month MACE among each treatment group

	All patients ($N=93$)	Homo-DES ($N=39$)	Hetero-DES ($N=26$)	POBA ($N=57$)
Overall MACE (%)	8.6 0.84 (0.75–0.91)	10.2 0.79 (0.63–0.90)	0	8.7 0.89 (0.77–0.95)
Death (%)	2.1 0.95 (0.88–0.98)	5.1 0.89 (0.74–0.96)	0	0
MI (%)	0	0	0	0
TVR (%)	6.4 0.89 (0.80–0.94)	5.1 0.94 (0.62–0.99)	0	7.0 0.89 (0.77–0.95)

Adjusted Kaplan–Meier survival probability estimate (95% CI). MI: myocardial infarction; TVR: target vessel revascularization.

Fig. 1



Kaplan–Meier survival curve. Number of patients at risk = 90.3%. Hetero-DES, drug-eluting stent implantation, eluted with the same drug; Homo-DES, drug-eluting stent implantation, eluted with the same drug; POBA, conventional balloon angioplasty.

18-month clinical follow-up. Kaplan–Meier survival probability (95% CI) showed that the HTD treatment group tended to have more favourable outcomes at 18 months, probably for differences in the endothelial response to the different DES, such that an initially poor response to one drug would be a signal to reimplant another DES with different mechanisms of action. Several treatment modalities have been proposed and used for in-stent restenosis: plain/cutting balloon angioplasty, vascular brachytherapy, rotational/directional atherectomy, excimer light amplification by stimulated emission of radiation (LASER)-based angioplasty and repeat stenting. Although POBA has been the most widely used treatment for ISR, it has been associated with high recurrent restenosis rates. Repeat stenting improves immediate results, but it has not been associated with acceptable mid-term and long-term outcomes [11–15]. On the contrary, there are no data to support the long-term advantage of ablative techniques [18–20]. In the RIBS (restenosis intrastent: balloon angioplasty versus elective stenting) study, POBA and restenting were comparable in terms of any MACE when BMS ISR was treated with another BMS [21]. DES has been established as the most successful treatment for the reduction of ISR risk in several patient and lesion subsets. A recent pooled analysis of two randomized studies (RIBS I and RIBS II) demonstrated that when compared with BMS, sirolimus-eluting stent (SES) improved the long-term clinical and angiographic outcome of patients with ISR. In particular, although inclusion/exclusion criteria were identical in the two studies, patients in the SES group had more adverse baseline characteristics, more diffuse lesions and smaller vessels. However, late angiographic findings, including in-segment recurrent restenosis rate, minimal lumen diameter and late loss were significantly better after SES [22]. Some registries and randomized trials showed that SES and PES were more effective than POBA and vascular brachytherapy in reducing recurrent restenosis rates after treatment of ISR [23–26]. A recent meta-analysis [27] analysed the results of four large randomized trials: the RIBS II (restenosis intrastent: ballon angioplasty versus elective sirolimus-eluting stenting II) [28], the SISR (sirolimus-eluting stent versus vascular brachytherapy for in-stent restenosis within bare-metal stent) [25], the ISAR-DESIRE (intracoronary stenting and angiographic results: drug-eluting stents for in-stent restenosis) [24] and the TAXUS-V ISR (prospective randomized trial evaluating slow-release formulation taxus paclitaxel-eluting coronary stent in the treatment of in-stent restenosis) [27]. The authors compared the performance of DES with POBA and vascular brachytherapy and demonstrated the superior efficacy of DES for BMS ISR in terms of target lesion revascularization (TLR). Although these important results regarding the rate of long-term revascularization, the incidence of MACE (a composite of death and MI) was not different between the two treatment groups.

Actually, few data are available about DES ISR management and many studies report a very high incidence of adverse cardiac events, both in lesions treated with 'sandwich DES' and POBA [16]. A recent study examined the outcomes of 92 consecutive patients who developed an ISR or DES thrombosis. These patients had been treated with 'sandwich stenting' (DES within the restenotic DES) divided into HMD and HTD or with other treatment techniques (including POBA and vascular brachytherapy). The 12-month clinical follow-up showed a very high rate of MACE (including death, MI and TLR) [16]. In contrast with these results, we have found an acceptable rate of MACE (8.8%) at 18-month follow-up in our overall population and, in particular, in the POBA group (8.7%). Notably, the rate of MACE observed in the present study is particularly low if we consider the complexity of our 'real word' population (high rate of patients with diabetes mellitus and multivessel coronary artery disease).

In another recent study, 174 patients who developed a DES restenosis within the previously stented segment were treated with a HTD or HMD. Overall MACE rate was 26% in HMD and 17.9% in HTD group, with a case of late thrombosis in the first group. The angiographic follow-up showed a TLR rate of 15.9 and 16% and a restenosis of 26.4 and 25.8%, in the HMD and HTD groups, respectively. The statistical analysis demonstrated a lack of association between the two types of

treatment and the incidence of MACE at follow-up [28]. Notably, in this study the POBA option was not considered as a default strategy for ISR management, not even for focal ISR. In our study, although there is not a significant difference in the three arms, POBA results in a very safe treatment, in particular when we have a focal in-stent restenosis (Mehran classification IA, IC).

Study limitations

Our observations were limited to the experience of a single centre. The absence of randomization to treatment strategy of ISR might also have influenced our results, even if in the analysis we considered the baseline characteristics. Another limitation of this study was the lack of angiographic follow-up after the ISR treatment.

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