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Original Research

Efficacy of Drug-Eluting Balloon in Patients with Bare-Metal or Drug-Eluting Stent Restenosis

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Percutaneous coronary intervention, in-stent restenosis, drug-coated balloon, coronary stent.

Introduction: In spite of improving results, the treatment of in-stent restenosis (ISR) of bare-metal stents (BMS), and particularly drug-eluting stents (DES), is a challenging clinical problem. There are promising but limited follow-up data concerning drug-eluting balloons in the treatment of BMS and DES restenosis. The goal of this real-world registry was to assess the long-term safety and efficacy of drug-eluting balloons in the treatment of BMS and DES restenosis.

Methods: In this prospective registry, 82 patients with BMS or DES restenosis treated with paclitaxel-eluting balloons were enrolled. The primary endpoint was ischemia-driven target lesion revascularization (TLR); a secondary endpoint was the rate of major adverse cardiac events (MACE) at 28 months.

Results: Thirty-five patients (42.7%) had DES ISR and 16 patients (19.5%) presented with an acute coronary syndrome. The success rate of drug-eluting balloon inflation was 97.6%. The median (interquartile range) duration of follow up was 28.0 (25.0-30.3) months. The rate of TLR was 24.5%, and was not significantly higher in the DES-ISR group than in the BMS-ISR group: 29.0% vs. 21.1%, respectively (p=0.687). There were two cases of definite stent thrombosis in the BMS-ISR group and one probable subacute stent thrombosis in the DES-ISR group. The overall MACE rate was 37.0% and did not differ between the DES-ISR and BMS-ISR group (40.8% vs. 34.7%, respectively; p=0.994).

Conclusions: This real-world registry provided less favorable long-term results for drug-eluting balloons in the treatment of BMS restenosis and in DES restenosis, compared to the promising mid-term results of previous studies. The TLR rate was slightly but not significantly higher after DES restenosis compared to BMS restenosis treatment.

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Compared to the bare-metal stent (BMS) era, the rate of in-stent restenosis (ISR) has been reduced by the introduction of drug-eluting stents (DES); however, it remains a challenge for interventional cardiology after coronary stent implantation.[1-5] We know from clinical observations that a significant percentage of ISR cases present as acute coronary syndrome;[6,7] thus, the first-line challenge is to reduce the frequency of ISR by using modern drug-eluting stents with a proper implantation technique. In cases where ISR develops, more therapeutic options are available. There are reports of high pressure balloon angioplasty, additional stent (commonly DES) implantation,[8-11] and some more sophisticated methods, such as intravascular brachytherapy and laser-based therapy, but their long-term angiographic and hemodynamic results proved to be less promising.[12-14] However, it is well known that re-restenosis in a previously restenotic stent, even treated by balloon angioplasty or stenting, usually represents a more complex clinical and angiographic situation with a poorer outcome.[15]

The concept of stentless drug delivery to the coronary wall combines the ad-

vantages of a well-controlled local drug action without acute and chronic inflammation triggered by the stent components. In the recent past, there have been several reports of drug-eluting balloons showing a potential beneficial effect in ISR treatment.[16-23] Although the first target of this kind of invasive treatment was the ISR, recent studies confirmed the efficacy of drug-eluting balloon treatment in *de novo* lesions,[24] as well as in small vessels[25] and in bifurcation coronary stenosis.[26] There is one trial, nevertheless, that failed to confirm the superiority of drug-eluting balloons in thrombotic coronary lesions followed by BMS implantation, compared to BMS only, in patients with ST-elevation myocardial infarction.[27] These results, generally supported by small cohorts of patients, make the need for real-life experience more pronounced.

The aim of our prospective registry was to evaluate the efficacy and safety of drug-eluting balloon treatment in BMS and DES restenosis.

Methods

Study population

The clinical and angiographic data of 82 consecutive patients treated by drug-eluting balloon for coronary ISR between May 2009 and March 2011 were evaluated in a prospective registry at the high-volume catheter laboratory (>1500 interventions/year) of Semmelweis University Heart Center. All patients entered in our registry underwent coronary dilatation with a drug-eluting balloon for hemodynamically significant ISR presenting as acute coronary syndrome or stable angina. There were no exclusion criteria. The enrolled patients were informed about the database and the processing of their relevant clinical baseline and follow-up data before they gave written consent. The local Ethics Committee provided ethical approval for this study, which satisfied the principles of the Declaration of Helsinki.

Coronary angiography

The coronary angiography was performed according to international recommendations, using the radial approach by preference. Every stenosis localized within the edges of a stent was measured from at least two views, without shortening of the current segment, by two skilled independent interventional cardiologists. Significant stenosis was considered to be present if the diameter stenosis was >50% in at least one of the views of the observed coronary segment. A conventional balloon was used for predilation of the target lesion. The recommended balloon-to-artery ratio was 1:1 and the balloon used was 5 mm shorter than the drug-eluting study balloon. During the procedures, three different types of paclitaxel-eluting balloons were used: SeQuent Please (B. Braun Melsungen AG, Berlin, Germany), Dior (Eurocor GmbH, Bonn, Germany), and Pantera Lux (Biotronik, Berlin, Germany). The choice among these balloon types was left to the discretion of the operators. The recommended inflation time of the drug-eluting balloon was 45 seconds for the Pantera Lux balloon, and 60 seconds for both the Dior and the SeQuent Please balloon. The procedure was evaluated as successful if the residual stenosis was <30% and no coronary dissection or occlusion was visible. In the case of dissection an additional stent was implanted.

Study definitions

The primary endpoint was clinically driven target lesion revascularization (TLR). Patients who underwent repeat percutaneous coronary intervention or bypass surgery for myocardial ischemia caused by ≥50% diameter stenosis within or 5 mm proximal or distal to the drug-eluting balloon treated stent were deemed to have TLR. The grade of in-stent restenosis was estimated visually. The secondary endpoint was major adverse cardiac events (MACE): the composite endpoint of all-cause death, definite and probable stent thrombosis, myocardial infarction and TLR. Stent thrombosis was defined according to the Academic Research Consortium criteria.[28] Stent thrombosis included both definite and probable categories. Stent thrombosis was defined as acute if it occurred during the first 24 hours, subacute in the first 30 days, late after one month, and very late if it occurred more than one year after the percutaneous coronary intervention. Periprocedural myocardial infarction (during the first 48 hours) was defined as a creatine-kinase-MB isoenzyme elevation to more than 3 times the upper range limit. After the periprocedural period, any elevation of troponin T above the upper range limit was considered as myocardial infarction. An independent panel of physicians, blinded to the procedural information, verified the clinical events using the source documentation.

Antithrombotic regimen

All patients received a loading dose of 300 mg of aspirin and 600 mg of clopidogrel before or at the time of the procedure, if they were not already on maintenance therapy. During the procedure, unfractionated heparin (100 U/kg body weight) was administered to every patient. Glycoprotein IIb/IIIa antagonists were used at the operators' discretion. Clopidogrel 75 mg daily was recommended for at least 6 months and aspirin 100 mg daily was continued indefinitely.

Follow up

Clinical follow up was performed 2 months after the index procedure, then once every 5 months in the outpatient clinic or by telephone contact. If a patient was lost to follow up, the National Insurance Fund was contacted. No routine angiographic check was performed.

Statistics

Categorical variables are expressed as absolute numbers and percentages, while continuous variables are given as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the parametric Student t-test. Survival curves were constructed by the Kaplan–Meier method and a log-rank test was performed to compare them. A multivariable Cox proportional-hazards model was used to identify independent predictors of TLR and MACE in patients with DES or BMS ISR. A stepwise multivariate analysis was performed using the variables presented in Table 1 and the type of drug-eluting balloon, type of arterial approach, angiographic pattern of the ISR (focal or diffuse/occlusive), and the type of stent (BMS or DES) in which the ISR developed. A p-value <0.05 was considered statistically significant. PASW 18.0 (IBM Corporation New York, USA) statistical software was used for all statistical calculations.

Results

Baseline demographic data

The enrolled patient population contained 82 subjects; 48.7% were male and the mean age was 63.4 ± 10.3 years. The typical study individual was affected by several cardiovascular risk factors and extensive coronary artery disease. The frequency of diabetes mellitus was 36.6%, 70.7% had a previous myocardial infarction, and 19.5% of the patients presented with an acute coronary syndrome, defined as unstable angina, non ST-elevation myocardial infarction or ST-elevation myocardial infarction. Although some of the patients with acute coronary syndrome suffered from low cardiac function, no intra-aortic balloon pump insertion was needed. The detailed baseline conditions are shown in Table 1.

All drug-eluting balloon dilatations were performed inside an in-stent restenosis; 42.7% of the cases were DES restenosis and 57.3% were BMS restenosis. Sixteen of the 35 DES restenosis patients had restenosis in first generation DES (Cypher or Taxus) and the other 19 in second generation DES (Endeavor, Promus, Xience). The type of anti-restenotic

Table 1. Baseline demographic data.

	Entire registry	BMS-ISR (n=47)	DES-ISR (n=35)	p
Age (years)	63.4 ± 10.3	63.6 ± 10.2	62.7 ± 10.9	0.569
Men, n (%)	40 (48.7)	24 (51.1)	16 (45.7)	0.632
Diabetes mellitus, n (%)	30 (36.6)	18 (38.3)	12 (34.3)	0.709
Arterial hypertension, n (%)	81 (98.8)	46 (97.9)	35 (100.0)	0.385
Dyslipidemia, n (%)	74 (90.2)	41 (87.2)	33 (94.3)	0.287
Current smoker, n (%)	19 (23.2)	11 (23.4)	8 (22.9)	0.954
Peripheral arterial diseases, n (%)	16 (19.5)	7 (14.9)	9 (25.7)	0.221
Renal failure, n (%)	7 (8.5)	4 (8.5)	3 (8.6)	0.992
Previous myocardial infarction, n (%)	58 (70.7)	36 (76.6)	22 (62.9)	0.176
Previous CABG, n (%)	12 (14.6)	3 (6.4)	9 (25.7)	0.014
Family history of CAD, n (%)	9 (11.0)	5 (10.6)	4 (11.4)	0.910
Acute coronary syndrome, n (%)	16 (19.5)	11 (25.6)	5 (14.3)	0.306

CABG – coronary artery bypass surgery; CAD – coronary artery disease.

drug eluted by the stent was sirolimus in 8 patients, paclitaxel in 8 patients, zotarolimus in 4 patients, and everolimus 15 patients.

Finally, in 82 patients, 82 equal ISR lesions were treated with inflation of 82 drug-eluting balloons. The most common ISR pattern[29] was the diffuse intra-stent pattern (35.4%), while the total rate of diffuse intra-stent, diffuse-proliferative and total occlusion ISR pattern was 46.4%. ISR in the right coronary artery (n=34) or left anterior descending coronary artery (n=28) was the most frequent target of the intervention; however, some cases presented with lesions in the left main stem (n=4), left circumflex coronary artery (n=16), or *ramus intermedius* (n=1). In 3 cases, the original stenting had been performed in a venous bypass graft. The rate of three-vessel disease ran as high as 28.0%. Angiographic data are shown in Table 2.

No routine intravascular ultrasound examination was done, while probable stent malapposition, as a commonly believed cause of ISR, was treated by high pressure non-compliant balloon inflation to the size of the proximal reference diameter in all cases.

Procedural results

The technical success rate of drug-eluting balloon inflation was 97.6%. In the remaining 2.4% (2 cases), drug-eluting balloon rupture occurred prematurely. In one of the 2 cases, further non-compliant balloon dilatation was needed because of residual in-stent restenosis. In the other case a DES was implanted. In another 3 cases, the angiographic results were not acceptable after drug-eluting balloon inflation. In 2 cases additional stent implantation was performed to treat dissection. In 1 further case, significant stenosis remained inside the treated stent, requiring high pressure dilation with a conventional balloon. The overall procedural success rate was 93.9%. The most frequently used drug-eluting balloon was Pantera Lux, in 73.2%, followed by Dior in 18.3% and SeQuent Please in 8.5%. (See procedural data in Table 3.)

Clinical follow up

The median length of follow up was 28.0 (25.0-30.3) months. The MACE rate reached 19.5% at 12 months and 37.0% at 28 months. The rates of all-cause death were 6.1% and 12.3%, of myocardial infarction 2.5% and 9.0%, and of TLR 12.7% and 24.5%, at 12 and 28 months, respectively. Two definite cases of stent thrombosis occurred: one was caused by a dissection within 24 hours after DEB intervention in a BMS restenosis; the other was a very late stent thrombosis in a BMS implanted in a bifurcation lesion. One unex-

Table 2. Angiographic characteristics.

	Entire registry	BMS-ISR (n=47)	DES-ISR (n=35)	p
BMS ISR, n (%)	47 (57.3)	47 (100.0)	-	-
DES ISR, n (%)	35 (42.7)	-	35 (100.0)	-
Previous stent diameter (mm)	3.0 ± 0.4	3.0 ± 0.4	3.0 ± 0.4	0.542
Previous stent length (mm)	26.3 ± 15.6	23.1 ± 10.5	29.9 ± 19.4	0.069
Angiographic pattern of ISR				
IB Stent margin, n (%)	6 (7.3)	3 (6.4)	3 (8.6)	0.706
IC Stent body, n (%)	25 (30.5)	12 (25.5)	13 (37.1)	0.259
ID Multifocal, n (%)	13 (15.9)	9 (19.1)	4 (11.4)	0.344
II Diffuse intra-stent, n (%)	29 (35.4)	16 (34.0)	13 (37.1)	0.772
III Diffuse-proliferative, n (%)	4 (4.9)	2 (4.3)	2 (5.7)	0.762
IV Total occlusion, n (%)	5 (6.1)	5 (10.6)	0 (0.0)	0.047
LM, n (%)	4 (4.9)	1 (2.1)	3 (8.6)	0.180
LAD, n (%)	28 (34.2)	14 (29.8)	14 (40.0)	0.335
CX, n (%)	16 (19.5)	10 (21.3)	6 (17.1)	0.640
IM, n (%)	1 (1.2)	1 (2.1)	0 (0.0)	0.385
RCA, n (%)	34 (41.5)	20 (42.6)	14 (40.0)	0.816
VBG, n (%)	3 (3.7)	2 (4.3)	1 (2.9)	0.739
True bifurcation lesion, n (%)	3 (3.9)	1 (2.1)	2 (6.5)	0.392
Small vessel (≤2.5 mm), n (%)	14 (17.1)	11 (23.4)	3 (8.6)	0.078
Treated vessel/patient, n/n	82/82	47/47	35/35	1.000
Three-vessel disease, n (%)	23 (28.0)	10 (21.3)	13 (37.1)	0.114

BMS – bare metal stent; DES – drug-eluting stent; ISR – in-stent restenosis; LM – left main coronary artery; LAD – left anterior descending coronary artery; CX – circumflex coronary artery; IM – *ramus intermedius*; RCA – right coronary artery; VBG – vein bypass graft.

plained sudden death two days after the procedure was observed in the DES-ISR group and was subsequently classified as probable stent thrombosis. The angiographic follow-up rate was 51.2%. Clinical follow-up data are shown in Table 4. There were no significant differences between the types of drug-eluting balloons as regards the clinical endpoints: TLR (p=0.467), MACE (p=0.633). See Table 5 for details.

Predictors of MACE and TLR

During the 28-month follow up we found two independent predictors of MACE and TLR by multivariate Cox analysis. Diffuse or occlusive type of restenosis was a significant predictor of TLR, with a hazard ratio of 2.070 (95% CI 1.047-4.093; p=0.036) and a significant predictor of MACE, with a hazard ratio of 2.056 (95% CI 1.101-3.838; p=0.024). Renal insufficiency independently predicted a higher rate of TLR, hazard ratio 9.618 (95% CI 1.710-54.094; p=0.010), and a higher rate of MACE, hazard ratio 7.810 (95% CI 2.691-22.667; p<0.001). Diabetes and the type of the treated DES had no independent effect on TLR or MACE in this setting.

BMS versus DES restenosis

It is well-known that DES restenosis is different from BMS restenosis regarding the underlying mechanism, angiographic pattern and appearance. More-

Table 3. Procedural data.

	Entire registry	BMS-ISR (n=47)	DES-ISR (n=35)	p
Radial approach, n (%)	68 (82.9)	41 (87.2)	27 (77.1)	0.223
Predilation (conventional), n (%)	82 (100.0)	47 (100.0)	35 (100.0)	1.000
Predilation (cutting), n (%)	1 (1.2)	0 (0.0)	1 (2.9)	0.244
Thrombus aspiration, n (%)	2 (2.4)	2 (4.3)	0 (0.0)	0.217
IVUS use, n (%)	3 (3.7)	1 (2.1)	2 (5.7)	0.392
Number of DEB treated lesions, n	82	47	35	
DEB/patient ratio, n/n	82/82	47/47	35/35	1.000
Type of DEB				0.316
- Dior, n (%)	15 (18.3)	9 (19.1)	6 (17.1)	
- SeQuent Please, n (%)	7 (8.5)	1 (2.1)	6 (17.1)	
- Pantera Lux, n (%)	60 (73.2)	37 (78.7)	23 (65.7)	
DEB diameter (mm)	3.08 ± 0.42	3.02 ± 0.43	3.16 ± 0.38	0.110
DEB length (mm)	22.8 ± 5.2	22.7 ± 5.1	23.0 ± 5.4	0.799
Inflation time (s)	49.0 ± 6.7	48.2 ± 6.2	50.1 ± 7.2	0.204
Kissing dilation, n (%)	3 (3.7)	1 (2.1)	2 (5.7)	0.392
Successful DEB inflation, n (%)	80 (97.6)	46 (97.9)	34 (97.1)	0.832
Postdilation after DEB, n (%)	2 (2.4)	0 (0.0)	2 (5.7)	0.097
Bailout stent implantation, n (%)	3 (3.7)	3 (6.4)	0 (0.0)	0.128
- Coronary dissection, n (%)	2 (2.4)	2 (4.3)	0 (0.0)	0.217
- Acute recoil (stenosis≥50%), n (%) (%)	1 (1.2)	1 (2.1)	0 (0.0)	0.385
Angiographic success, n (%)	77 (93.9)	44 (93.6)	33 (94.3)	0.900

IVUS – intravascular ultrasound; DEB – drug-eluting balloon.

Table 4. Follow-up data of entire registry at 28 months; BMS-ISR and DES-ISR subgroups at 12 and 28 months.

	Overall	BMS-ISR 12 month	DES-ISR 12 month	BMS-ISR (n=47) 28 month	DES-ISR (n=35) 28 month	p
Overall death, n (%)	10 (12.3)	4 (8.5)	1 (2.9)	6 (12.9)	4 (11.4)	0.828
ST, n (%)	3 (3.8)	1 (2.1)	1 (2.9)	2 (4.5)	1 (2.9)	0.724
AMI, n (%)	6 (9.0)	2 (4.4)	0 (0.0)	4 (9.5)	2 (8.8)	0.620
TLR, n (%)	18 (24.5)	6 (13.3)	4 (11.8)	9 (21.1)	9 (29.0)	0.687
MACE, n (%)	29 (37.0)	11 (23.4)	5 (14.3)	16 (34.7)	13 (40.8)	0.994
Angiographic follow-up rate, n (%)	42 (51.2)	14 (29.8)	14 (40.0)	24 (51.1)	18 (51.4)	0.211

ST – (definite and probable) stent thrombosis according to Academic Research Consortium; AMI – acute myocardial infarction; TLR – ischemia driven target lesion revascularization; MACE – major adverse cardiac events.

Table 5. Follow-up data at 28 months according to type of drug-eluting balloon.

	Entire registry	Dior (n=15)	SeQuent Please (n=7)	Pantera Lux (n=60)	p
Overall death, n (%)	10 (12.3)	2 (13.3)	1 (14.3)	7 (11.8)	0.971
ST, n (%)	3 (3.8)	1 (6.7)	0 (0.0)	2 (3.5)	0.687
AMI, n (%)	6 (9.0)	1 (6.7)	0 (0.0)	5 (11.0)	0.715
TLR, n (%)	18 (24.5)	2 (14.4)	2 (28.6)	14 (26.1)	0.710
MACE, n (%)	29 (37.0)	4 (26.7)	2 (28.6)	23 (40.9)	0.716
Angiographic follow-up rate, n (%)	42 (51.2)	6 (40.0)	5 (71.4)	31 (51.7)	0.008

ST – (definite and probable) stent thrombosis according to ARC; AMI – acute myocardial infarction; TLR – ischemia driven target lesion revascularization; MACE – major adverse cardiac events.

over, DES restenosis reacts differently to treatment than does BMS restenosis. Baseline demographic and angiographic data were somewhat different in the following ways: the rate of previous bypass surgery was significantly higher (25.7% vs. 6.4%, p=0.014) and the previous implanted stent length was slightly higher (29.9 ± 19.4 vs. 23.1 ± 10.5 mm, p=0.069) in our patient population, while no patient in the DES-ISR group had occlusive restenosis (0.0% vs. 10.6%, p=0.047). There were no differences between the DES-ISR and BMS-ISR groups regarding the clinical endpoints. (See details in Table 4.) The Kaplan–Meier TLR-free and MACE-free survival rates were slightly lower after the first year in the DES-ISR group; these curves are shown in Figures 1 and 2.

Discussion

Our single-center prospective registry represents a kind of evidence of the efficacy of drug-eluting balloon treatment in patients with BMS and DES restenosis. The Pantera Lux, SeQuent Please, and Dior balloons we used proved to be effective during the first year, as the rate of TLR was below 14% in both BMS-ISR and DES-ISR groups. The increase in the next 16 months was 7.8% versus 17.2% in the BMS-ISR versus DES-ISR group, respectively. However, the results were less favorable after 28 months of follow up, given the continuous increase in TLR, particularly in the DES-ISR group. Our findings confirmed the so-called late catch-up phenomenon among pa-

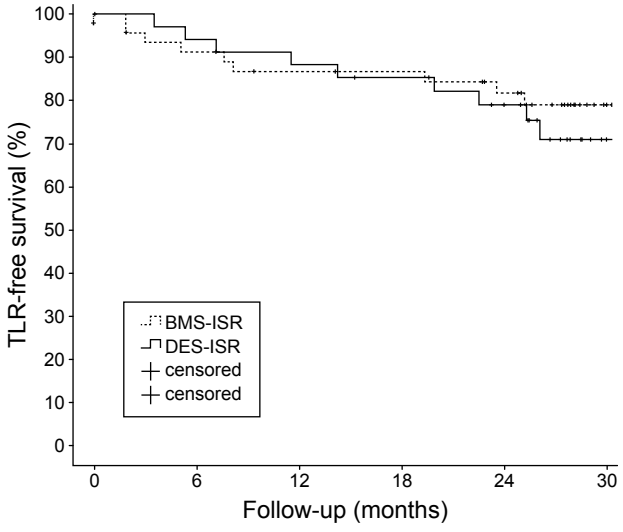

Figure 1. Kaplan–Meier survival curve for target lesion revascularization (TLR) in the BMS-ISR and DES-ISR groups. TLR rate was 21.1% versus 29.0% at 28-month follow up in the BMS-ISR versus DES-ISR group, respectively (log-rank p=0.687).

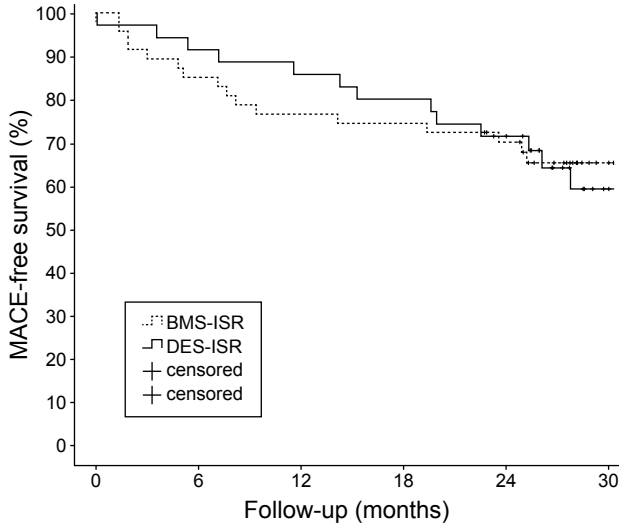

Figure 2. Kaplan–Meier survival curve for major adverse cardiac events (MACE) in the BMS-ISR and DES-ISR groups. The total MACE rate was 34.7% versus 40.8% at 28-month follow up in the BMS-ISR versus DES-ISR group, respectively (log-rank p=0.994).

tients treated with drug-eluting balloons because of DES restenosis, as we found the TLR rate to be more than double after one year of follow up. Sgueglia et al, in a meta-analysis of TLR after drug-eluting balloon treatment of DES restenosis, observed almost a doubling of the rate between 6 and 12 months' follow up, whereas the TLR rate remained stable over the same period after BMS restenosis treatment.[30]

The investigated patients had a high risk of restenosis, with high rates of diabetes mellitus and three-vessel disease, and an ISR pattern of diffuse, diffuse-proliferative and total occlusion. A slightly higher TLR and MACE rate, though not significantly so, was found in the DES ISR group compared to the BMS ISR group after drug-eluting balloon inflation during long-term clinical follow up, although the sample sizes of the subgroups were relatively small.

Our first-year results are comparable with those of recently published registries. The Spanish DIOR multicenter registry showed an 11.9% TLR rate at 1-year follow up of patients who underwent drug-eluting balloon treatment after DES and BMS ISR.[19] The TLR rate was slightly higher in the case of DES ISR (14.8% vs. 9.2%; p: NS). The SeQuent Please World Wide Registry, which is currently the largest drug-eluting balloon registry, yielded a higher TLR rate after DES ISR treatment compared to BMS ISR treatment (9.6% vs. 3.8%; $p<0.001$), after 9.4 months of follow up. The difference between outcomes may be a consequence of local antiproliferative drug resistance in the DES population, while in case of BMS ISR lesions the local drug therapy may have had a positive response.

Mechanisms of BMS and DES ISR

BMS eliminated the main grounds for restenosis after balloon angioplasty, but neointimal hyperplasia remained the main cause of BMS ISR. DES, with their antiproliferative drug release, inhibit this undesirable process, although this drug also defers the endothelization of the stent surface, thus prolonging the risk of stent thrombosis. DES ISR is no longer a rare entity, due to the fact that DESs are implanted into far more complex lesions and to adverse phenomena such as stent underexpansion/malapposition, drug failure, or strut fracture.[7]

Management of BMS and DES ISR

The invasive management of a coronary artery with ISR, even in the previous standard treatment with BMS, remains challenging. Some randomized studies comparing DES with balloon angioplasty,[8,9] or even with brachytherapy,[12-14,31] and real life experience with DES in the treatment of BMS ISR[11] from the near past, all proved the beneficial use of DES in patients with BMS ISR. The rate of TLR after DES therapy ranges between 10.1% and 19.0% during long-term follow up. In these trials, the effectiveness of balloon angioplasty and brachytherapy regarding TLR was outperformed by DES. However, the relatively high numbers of repeat ISR in DES after ISR treatment may raise some questions about the usefulness of the method.[15] Drug-eluting balloons have a favorable effect on BMS ISR treatment without a new stent layer inside the ISR. The PACCOCATH ISR II randomized multicenter trial revealed a reduced repeated TLR rate after drug-eluting balloon treatment of ISR at 2 years (6.0% vs. 37.0%) and at 5 years (9.3% vs. 38.9%), where conventional balloon angioplasty was the comparator.[16,17] In the PEPCAD II study, the SeQuent Please drug-eluting balloon was compared to the Taxus paclitaxel-eluting stent as treatment options after BMS ISR. The study revealed that there was no statistically significant difference in 1-year MACE between the two modalities; however, the in-segment late loss (0.17 ± 0.42 mm vs. 0.38 ± 0.61 mm) and binary restenosis rate (7% vs. 20%) of the drug-eluting balloon group were superior to those of the Taxus DES.[18]

On the other hand, there are observations suggesting that the treatment methods that were successfully utilized in BMS ISR received a different response in DES ISR. The study of Steinberg et al demonstrated that DES implantation is less favorable in DES ISR compared to BMS ISR, with target vessel revascularization rates at 1 year of 22.2% vs. 10.3%, respectively.[10] To treat DES ISR, the ISAR-DESIRE 3 trial confirmed that the drug-eluting balloon is not inferior to a paclitaxel-eluting stent in terms of restenosis, while both were superior to balloon angioplasty: the rates of TLR were 22.1% vs. 13.5% vs. 43.5%, respectively.[22] Other studies, such as PEPCAD-DES (TLR 15.3% vs. 36.8%) and the investigation by Habara et al (TLR 4.3% vs. 41.7%), also confirmed the superiority of drug-eluting balloon over plain balloon angioplasty during 6-month follow up.[20,21] Even so there is only a small amount of evidence proving the advantages of drug-eluting balloon treatment in ISR regarding the clinical outcome. Some issues are still not clearly understood, such as the patient selection for drug-eluting balloon therapy

and the factors that may influence the long-term success rate in the future.

Summary

The use of drug-eluting balloons is considered to be one of the potentially beneficial methods in settings of ISR in either BMS or DES. Our results demonstrate a good mid-term and moderate long-term clinical success rate in patients with high cardiovascular risk, with cumulative ischemia-driven TLR rates of 12.7% and 24.5% and MACE rates of 19.5% and 37.0% at 12 and 28 months, respectively. In this registry we found slightly less favorable results in patients with DES ISR compared to BMS ISR beyond one year. However, randomized clinical trials and larger patient population registries with longer follow-up durations will be required to prove the effectiveness of drug-eluting balloons in ISR lesions.

Promising "stentless" percutaneous coronary intervention techniques

Recently, two new options have been devised to tackle the problem of ISR. Besides the drug-eluting balloon, which is a stentless delivery system of a locally acting cytostatic drug, the other promising opportunity is the drug-eluting bioabsorbent vascular scaffolding, which offers all the necessary advantages to effectively reduce or eliminate ISR. Although the preliminary clinical observations are promising,[32] we should still wait for the longer-term results from a larger number of patients.

Limitations

This study was a non-randomized single-center registry. The primary endpoint was clinically driven TLR; hence, no routine control angiography was performed. Lesions were estimated visually. This registry was underpowered to detect differences in clinical outcomes between the three types (Dior, SeQuent Please and Pantera Lux) of drug-eluting balloons. During the procedures, routine intravascular ultrasound imaging was not performed.

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